A STUDY OF PREVALENCE AND CLINICAL CORRELATES OF NICOTINE DEPENDANCE IN SCHIZOPHRENIA IN DEPARTMENT OF PSYCHIATRY, TIRUNELVELI MEDICAL COLLEGE HOSPITAL

Dissertation submitted to

THE TAMIL NADU DR. M. G. R. MEDICAL UNIVERSITY

in part fulfillment of the requirements for

DOCTOR OF MEDICINE

(BRANCH – XVIII) PSYCHIATRY

EXAMINATIONS – APRIL 2013

DEPARTMENT OF PSYCHIATRY,

TIRUNELVELI MEDICAL COLLEGE AND HOSPITAL,

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DECLARATION

I, Dr. M.Amali Victoria, solemnly declare that this dissertation **"A STUDY OF PREVALENCE AND CLINICAL CORRELATES OF NICOTINE DEPENDANCE IN SCHIZOPHRENIA IN DEPARTMENT OF PSYCHIATRY, TIRUNELVELI MEDICAL COLLEGE HOSPITAL"** was done by me at the Department of Psychiatry, Tirunelveli Medical College, Tirunelveli under the guidance and supervision of the Professor of Psychiatry, Tirunelveli Medical College, Tirunelveli between March 2011 and September 2012.

This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai – 32 in partial fulfilment of the University requirements for the award of the degree of M.D., Psychiatry.

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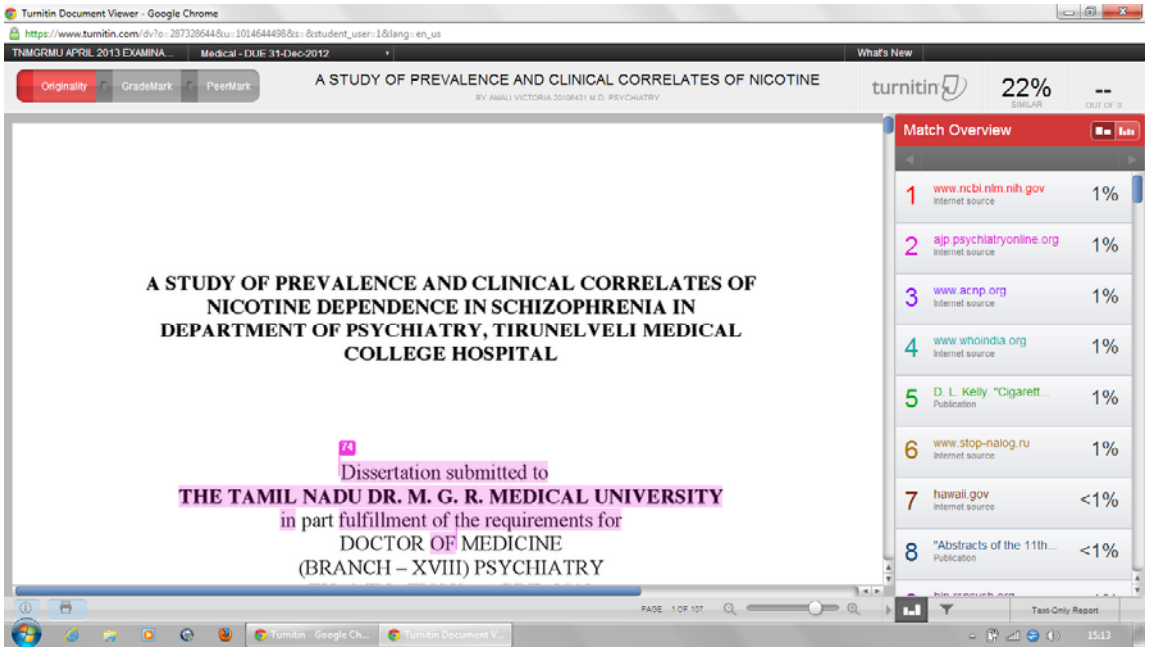
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INDEX

INTRODUCTION

The health problems associated with smoking tobacco are well known which include both the acute symptoms such as cough, dyspnea,throat irritation,frequent lower respiratory tract infections and the increased risk of developing chronic and serious medical conditions such as bronchogenic carcinoma, heart disease , exacerbation of chronic obstructive pulmonary diseases like chronic bronchitis,bronchiectasis,bronchial asthma and emphysema ,aggravation of thrombo-embolic phenomena like stroke,myocardial infarction,Thrombo-angitis Obliterans etc. Apart from the medical complications involving the respiratory tract, people who smoke cigarettes tend more frequently to have oral, nose, and throat cancer due to inhalation of the smoke than it is among the nonsmokers of the same age group.

Patients diagnosed as schizophrenia are much more likely to smoke , the prevalence being approximately 70 percent as against 30 percent in the general adult population . Earlier studies on this proposed that the higher rates of smoking and use of smokeless tobacco among schizophrenic patients might be a reflection of their effort to subjectively remediate cognitive dysfunction by themselves[1] .Many different

explanations have been proposed for this high prevalence,however a matrix of causes have been implicated namely neurological, behavioral, psychological and environmental factors.

Smoking being a very common pattern of behaviour among patients with schizophrenia is also an important modifiable risk factor that contributes to medical mortality. It has been found that Schizophrenic patients also tend to be heavier smokers. In the Clinical Antipsychotic Trials of Intervention Effectiveness(CATIE)[2] study a total of 68 percent of schizophrenia patients were nicotine dependent.

Both the morbidity and the mortality caused by cardiovascular diseases are found to be much higher in people with schizophrenia irrespective of their treatment status than in the general population[3]. Dyslipidaemia is an established risk factor for cardiovascular disease along with hypertension, diabetes, obesity, smoking and a sedentary lifestyle. The majority of patients with schizophrenia have several of these risk factors and can be considered to be having a higher propensity to develop cardiovascular diseases.

The most important cardiovascular cause of mortality in schizophrenic patients is coronary heart disease [4]. In a study by Goff et al in 2005 comparing the risk of cardiovascular risk among those patients from the follow up of CATIE study and controls it was found that schizophrenic individuals had a greater ten year risk of developing

cardiovascular diseases in comparison to the general population in respect for both sexes : male schizophrenics developing at a rate of 9.4% vs a rate of 7.0% in the general population males and female schizophrenics at a rate of 6.3% vs a rate of 4.2% in the general population females [5] .Moreover one other recent report notes that the mortality ratio for cardiovascular death is about 3 times the general population ratio in schizophrenic patients.[6]

Apart from the high morbidity and mortality in persons who smoke, combined with a high propensity to develop metabolic syndrome in schizophrenic patients on antipsychotics for a prolonged duration, these patients are at a very high risk to develop cardiac and lung diseases.Though there have been numerous studies in the west that looked into the medical co-morbidities in schizophrenic patients there is a huge paucity in our Indian studies.

The World Health Organisation proposes that about 13% of all deaths among Indians by the year 2020 would be linked to the association between the use of tobacco and infections like tuberculosis, lung cancer, other chronic lung diseases and cardiovascular diseases .Thus we see that the human health and economical burden of using tobacco for a densely populated country like India with highly effective marketing strategies for tobacco related products are strikingly high.This underscores the need for immediate attention to curb the tobacco related harmful

consequences in people of all age groups especially among the more susceptible mentally ill .

Further smoking being the most commonly used,cheap,freely available ,less stigmatizing substance of abuse may serve as a gateway for the onset of a huge array of substance abuse.The **gateway drug theory** also known as **gateway effect /gateway theory/ gateway hypothesis** states that persons who start using less deleterious drug of dependance run a high future risk of using more dangerous hard drugs and/or crime .This theory has often been used to explain polysubstance abuse of many drugs including tobacco, alcohol and cannabis.This very much applies to the mentally ill population who are at the greatest risk for substance dependance.

Rationale for this study:

It is necessary to address this comorbidity of substance use in schizophrenic patients because of its association with poorer clinical and social outcomes and it significantly contributes to their morbidity and mortality . Overall, substance-use disorders are a harbinger of a worser course and outcome of all severe psychiatric illnesses by causing more frequent relapses ,the higher need for hospitalizations, poor psychosocial functioning even after control of active symptoms and more of legal, health and housing problems.

There have been studies conducted in the United states,the Spanish population and in Chinese population.However such a study of this kind has not been carried out in our Indian population.This prompted us to perform this study to look into the extent of nicotine dependence among our population and to see its effect on the positive and negative symptoms of schizophrenia, its association with antipsychotic dosing in these patients and its effect on medication induced movement disorders.

REVIEW OF LITERATURE

HISTORY OF NICOTINE

In 1512, the tobacco plant was introduced into Portugal, where it was used first by sniffing powdered leaves of the plant to relieve migraine and until 1559 their use in Europe has been limited to in this country .In 1560 Jean Nicot introduced tobacco as a wedding gift for the royal family at Paris. Later in 1570, the tobacco plant was officially named after him as Nicotiana tabacum. In 1828, nicotine was first isolated from nicotinic acid and was known as niacin or vitamin B .It was first synthesized in the laboratory in 1904[7].

FORMS OF SMOKING TOBACCO DEPENDANCE

Cigarettes or cigars, hookah tobacco,hand-rolled tobacco,snuff,gutka,chewing tobacco leads on to health problems, which may be ultimately fatal .There are various methods of smoking[8], which include many varieties of cigarettes, bidis, like, Hookah, Dhumti, reverse chutta, Chillum, cigars, cheroots and many flavors of chewing gum as Gutkha Khaini, Zarda, Gudhaku, paan (with smoking) Gul, Mawa, Mishri and some other forms as well.

Beedi

In India beedi is the most commonly used form of tobacco . India utilizes about thirty-five percentage of its tobacco for manufacturing beedi.

Beedi are flakes of dried tobacco which is rolled in a dried, rectangular piece of tendu leaves.

Cigarettes

These are the second most commonly used form of tobacco in India after beedis.It is used more frequently by the affordable population.

Cigars

Cigars are fermented tobacco cured by air, often manufactured in factories and are usually more expensive than beeidis and cigarretes. Cigar smoke is most used in urban settings in north India .It is rarely used these days in south India.

Chuttas and cheroots:

Chuttas which is a cylinder homemade from tobacco leaves. In India a huge quantity of chuttas are made every year as much as 3000 million units .Another mode of smoking chutta namely Reverse chutta smoking is being prevalent in some of the coastal areas of Tamil Nadu ,Andhra Pradesh and Orissa.

Pipe

Pipe smoking is an older form of tobacco use where they use small wooden rods or pipes ,long metal rod or other material.

Dhumti

It is another form of smoking tobacco but unlike beedi and chuttas ,dhumtis cannot be obtained from the routine suppliers of cigarettes, but are prepared by the consumers themselves. It is made by rolling cigar tobacco leaves in the sheets from another plant.

Hookah

The hookah is a type of pipe in India, where tobacco is smoked through water before inhalation.

Chillum:

It is a clay pipe filled with tobacco.It is used exclusively by males.Chillum was in use in India even before the use of tobacco for smoking other drugs like opium etc.

FORMS OF SMOKELESS TOBACCO DEPENDANCE

Most practices of chewing tobacco are more common in the north and northeastern India. "Smokeless tobacco" is the type of tobacco use in which tobacco is consumed without heating or burning while it is used[9]. It is either used orally or nasally. For nasal use the dry snuff which is fine tobacco powder layer mixed with aromatics is used. The other

methods of taking tobacco are by means of sucking,chewing and as applications of tobacco preparations on teeth and gums.

Paan is a form of betel with tobacco.Betel leaves contain volatile oils such as terpenes and eugenol ,small amounts of sugar, starch, tannin ,nitrates etc.Zarda are commercially manufactured varieties are often used as ingredients in paan.

Paan masala

Paan masala is a widely marketed commercial preparation containing areca nut, slaked lime, catechu and spices with or without powder tobacco.Paan masala is very popular in urban areas and is also fast becoming popular in rural areas. Other Tobacco, areca nut and slaked lime preparations include Mainpuri tobacco,Mawa

Tobacco and slaked lime (Khaini):it is a mixture of dried tobacco and slaked lime and is widely used in Maharashtra and also in several states in North India

Chewing tobacco

Snus

This snuff called snus is available in teabaglike sachets. Several preparations of smokeless tobacco as Mishri, gudhaku, bajjar and creamy snuff are first and foremost used as a powder to clean the teeth and gums. However in due course it turned out to be substances of dependance.

Gul is a pyrolysed tobacco product. Bajjar is a dry snuff.Traditionally few tobacco based toothpastes were introduced into the market , but after passing a law banning smoking in dental care products, the list of tobacco as an ingredient was stopped.

Gudhaku is made of a paste of tobacco and molasses.

Nicotine gum

Nicotine chewing gum with nicotine to 2% (good - kha) was introduced as an aid to smoking cessation. For chewers, it is in gutka flavor and smokers, mint flavor.

With reference to previous studies done in India , the dependency ratio for beedi cigarettes and chewing tobacco was 56%, 30% and 67%, respectively [10]. The rates of combined smoking and smokeless/chewing tobacco use was 45% . This value is a bit higher than that obtained by another Chennai based study done by Srinivasan(2002) which quotes a prevalence of 31.6% and even higher than that (33%) for the Indian males of the general population[11].

PATTERNS OF NICOTINE USE:

Most smokers begin their habit in their teens.The habit is mainly acquired through social contacts and the risk is increased if the family members and friends also smoke. Smokeless tobacco in the form of snuff or chewing tobacco forms a less frequent but sizeable portion of tobacco use. By making harder puffs, deeper or more frequent puffs they are able

to obtain significant amounts of nicotine from fewer cigarettes or from low nicotine cigarettes. Patterns may also depend on social factors. Suppression of smoking in forbidden areas like hospitals, religious places, aircrafts etc. forces smokers to alter their pattern of intake to accommodate the periods of deprivation. After a period of ***experimental smoking*** person enters a period of initiation when he smokes less than one cigarette per week. During experimental smoking peers often provide social reinforcement. Smoking for the adolescents serves as a means of expressing an image of toughness, precocity and sociability. Experimental inhalation is followed by ***habituation*** in which the person smokes atleast one cigarette per week and acquires the skill of inhalation and regulation of the dose of nicotine. With habituation the consumption may increase to a pack or more per day. Habituation progresses to the development of ***dependance.***

PHARMACOLOGY OF NICOTINE:

Nicotine is both a water and lipid soluble weak base .It has an index of ionization about 8.0.The nicotine which is present in the slightly alkaline smoke of cigars, pipes, snuff and chewing tobacco gets readily absorbed across the mucosal membranes of the mouth and nose [12]. However the more commonly used cigarette smoke is mildly acidic and is not well absorbed from the mouth and it has to be inhaled for effective

absorption. Thus the absorption of nicotine through the mucous membrane occurs in a highly pH dependent fashion .

PHARMACOKINETICS OF NICOTINE:

The cigarette tobacco is the most toxic and addictive widely used vehicle for delivery of nicotine . Nicotine present in cigarette smoke is suspended on minute particles of "tar" after getting distilled at the tip of a burning cigarette .This tar is absorbed quickly from the lung almost with the efficiency of IV administration.It reaches the brain within 0.8 seconds after inhalation. Cigarettes are also the source of carbon monoxide(CO) and many other toxic pyrolysis products. The nicotine absorbed in the lung alveoli is finally concentrated in the pulmonary veins and then pumped by the left ventricle of the heart throughout the body.

Nicotine gets absorbed from the respiratory tract, buccal membranes, and skin. Being a relatively strong base, the absorption of nicotine from the stomach is low whereas the absorption at the intestinal level is much more efficient.

An average cigarette contains approximately 6–11 mg nicotine . The smoker who smokes a pack per day thus obtains 20-40 mg of nicotine each day in total .The peak plasma concentrations of nicotine in

the plasma after a cigarette is smoked are typically 25-50 ng/ml. The half life is half an hour to 2 hours. The nicotine in chewing tobacco on the other hand because of its slower absorption than inhaled nicotine, tends to have a longer duration of effect. Further the nicotine bioavailability can be increased according to the technique and the intensity of puffing of the smoker. Regular smokers are able to very often without conscious knowledge or effort, calibrate the plasma concentrations by regulating the puff volume, inter-puff interval and the amount of smoke inhaled. This has been more so in the schizophrenic smokers in whom it is raised as much as threefold since these patients by the very nature of their disease tend to take longer and deeper puffs and thus extract very high quantities of nicotine from a single cigarette.Hence nicotine and tar intake cannot be determined accurately by the amount smoked since the dose is affected by the manner of smoking. The rate of nicotine absorption is rapid for cigarettes. However the nicotine level in the blood falls quickly since nearly 50% of it gets redistributed within twenty minutes of the last puff of cigarette.

METABOLISM :

Almost 80–90% of nicotine remains in an altered form in the body, mainly in the liver , kidney and lung and less than a 5% is excreted in the urine in an unchanged form . The major initial nicotine metabolite

is **cotinine**, which is about one-twentieth to one-hundredth as potent as nicotine [13]. Cotinine has been used as a marker for nicotine intake because it has a half life of half hour to 20 hours and can be easily measured in blood, urine, or saliva.

The harmful **Carbon monoxide (CO)** coming from the smoke of the cigarette with a half-life of 4-7 hours gets eliminated from the lung and it is a reliable and measurable function of respiration rate. Hence by measuring the expired air Carbon monoxide(CO) or Carboxyhaemoglobin(COHb) we can estmate the time lag of recent cigarette smoke exposure .

TOLERANCE

Tolerance occurs to an array of behavioral, physiological and subjective effects of nicotine. The mechanisms that underlie nicotine tolerance are decreased responsiveness to the drug ,increased number of nicotine receptors and some degree of increased metabolism . It has been found that cigarette smokers lose a sizeable degree of tolerance while they sleep each day which they attempt to regain upon resumption of smoking. A single nicotine exposure has the propensity to cause **tachyphylaxis**[14] which may be defined as a short-lived tolerance to the psychoactive, cardiovascular, and other effects of nicotine.

WITHDRAWAL SYNDROME:

It includes mood changes , difficulty concentrating, restlessness, insomnia, decreased heart rate and weight gain . The insomnia may be characterized by increased awakenings and intense dreaming. Post nicotine cessation weight gain may be explained by the increased eating and the loss of nicotine stimulation of metabolism. Craving is common and increased coughing, altered bowel movements in the form of constipation, oral ulcers and decreased performance on tests of vigilance tasks can occur.

This withdrawal syndrome is typically most severe for abstinence from ***cigarettes***, intermediate for abstinence from ***smokeless tobacco***, and least severe with abstinence from ***nicotine-replacement products.*** The withdrawal symptoms may vary for a duration of 1 to 3 days and may even last up to 2 to 3 weeks. The nicotine craving and weight gain can persist for even 6 months or more.

PHARMACODYNAMICS:

Nicotine causes release of catecholamines in the central nervous system (CNS) as well as of serotonin,ADH,corticotrophin and growth hormone.On the cardiovascular system ,the effects are those of sympathetic autonomic stimulation.There is vasoconstriction in the skin

and vasodilatation in the muscles,tachycardia and a rise in blood pressure of about 15mmHg systolic and 10mm Hg diastolic and increased plasma noradrenalin. Ventricular extrasystoles may occur and cardiac output ,work and oxygen consumption increase. Nicotine increases platelet adhesiveness ,an effect that may be clinically significant in atheroma and thrombosis. Nicotine increases metabolic rate and hence stopping of smoking may lead to weight gain in some individuals. Tolerance develops to some of the effects of nicotine taken repeatedly over few hours.

Nicotine is an agonist to receptors at the ends of peripheral cholinergic nerves whose cell bodies lie in the central nervous system i.e. it acts at the autonomic ganglia and at the voluntary neuromuscular junction. Higher doses paralyse the same points. The CNS is stimulated including the vomiting centre and tremors and convulsions may occur .However as with peripheral actions depression follows stimulation.

Cigarette smoke being powerful hepatic enzyme inducer rapidly metabolises many of the drugs which are normally metabolized by the liver.The implication of this is that patients may require a much higher doses of many drugs for treating their symptoms when they smoke heavily than that needed for the nonsmokers to obtain similar plasma levels. Apart from nicotine having pharmacodynamic effects, non - nicotine chemicals in tobacco smoke activate the cytochrome P450

enzyme systems, thereby decreasing the plasma levels of those medications that are normally metabolized in the liver. This explains that when a person stops smoking the concentrations of many of these medications increase which might precipitate many of the dose related adverse effects. Many of these medications being psychiatric medicines the increase in concentration can be clinically significant; for example, ***haloperidol , clozapine and fluvoxamine*** concentrations increase 30 to 40 percent with abstinence.

NEUROBIOLOGY OF NICOTINE ADDICTION

Nicotine diffuses into the brain tissue and gets bound to the nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels.The Nicotinic acetylcholine receptor complex is composed of 5 subunits which is found in both the peripheral and central nervous systems. The most abundant receptor subtypes present in human brains are α4 β 2, α 3 β 4, and α7 . The α 4 β 2 receptor subtype is the most predominant subtype among the three and is believed to be the main receptor mediating nicotine dependence.

The α 4 subunit is the receptor that determines the individual's sensitivity to nicotine. The α3 β 4 and the α 7 homomeric receptor subtypes are said to mediate the cardiovascular effects of nicotine. The α

7 subtype has been implicated in rapid synaptic transmission and is found to play a role in sensory gating and learning.

TOBACCO USE:

Tobacco use is the habitual use of any of the tobacco plant leaf and its products. The majority of persons with nicotine dependance use tobacco in the smoking form by using beedis, cigarettes, pipes, and cigars. Smokeless tobacco is the use of tobacco products by way of sniffing , sucking or chewing. Chewing tobacco the person places a portion of the tobacco between his cheek and gum or upper lip teeth fro sometime and then chews it. All the tobacco products contain the highly addictive psychoactive ingredient nicotine.

Updated studies show that there is a 30 to 80% higher total mortality in cigarette smokers when compared to nonsmokers. This increased mortality depends on the age at which the person begins to start smoking and on the average number of cigarettes that the person smokes in a day. Since schizophrenic patients have a much heavier abuse of tobacco, there is an increased risk for mortality in these patients. Further it has also been found from various studies that people aged 35–54 years who smoke more than one pack per day had an increase in the absolute mortality risk by 170% as compared to the non smokers. [15]

Early age at onset of smoking and using cigarettes which are higher in tar increases the risk of these diseases.The environmental tobacco smoke or secondhand smoke also causes varied adverse health effects in people of all ages due to the effects of passive smoking.

The cigarettes sold in underdeveloped countries tend to have higher tar content and are less likely to be filtered thus potentially increases the vulnerability to tobacco-related disease in these regions. Among the 4000 compounds that has been identified in cigarette smoke, constituents like tar, carbon dioxide, nitrous oxides, and nicotine are responsible for the major health hazards of smoking.

The smokeless tobacco also carries its own risk by its contents being rich in specific carcinogenic N-nitrosamines which are produced from nicotine, nornicotine, and anatabine during the curing and processing of the smokeless tobacco.

GLOBAL BURDEN OF TOBACCO

Almost 22% of the world's population aged more than 15 years are smokers**.**Among the 1.22 billion smokers in the world, 47% are men and 12% are women. In the developing countries the rates range from about 48% in men and about 7% in women, which might be because smoking has spread there only recently. Among the 1.22 billion smokers, 1 billion of them live in developing or transitional economies. It is said

that nearly 80% of the world's one billion smokers live in the low- and middle-income countries.

Globally 12% of all deaths among adults aged 30 years and over were attributed to tobacco.Tobacco kills almost one person every six seconds. It has been speculated that a third to half of all people who use it, die on average 15 years prematurely. Today, tobacco is said to use cause 1 in 10 deaths among adults worldwide –which amounts to more than five million people a year. And it is predicted that by 2030, unless urgent action is taken, tobacco's annual death toll is estimated to rise to more than eight million. [16]

And according to the World Health Organization (WHO), tobacco kills more people annually than does the problematic diseases like alcohol, AIDS, other addictions (drugs) and accidents put together.

TOBACCO BURDEN IN INDIA

There are approximately 120 million smokers in India, about 37 percent of all men and 5 percent of all women between the ages of 30 and 69. According to the study published in the New England Journal of Medicine[17], more than 50 percent of the tobacco-related deaths in India occur among illiterate men or women, and 80 percent of those people reside in rural India.

The WHO reports suggest at least one form of tobacco is used by 65% of all Indian men . The usage statistics for women differed grossly from as high as 67% in Andhra Pradesh to as low as 15% in rural Gujarat . The overall prevalence for bidi and cigarette smoking is 3% .It has been reported that fully one third of all women use at least one form of tobacco and used smokeless form in most instances[18]. About 58 % of women use tobacco in Mumbai solely in the smokeless form.

According to the National Sample Survey (NSS) in India, 15% consume cigarettes, 54% of tobacco consumers consume bidi, and 30% consume different chewing tobacco products.

It has been estimated that only 20% of the total tobacco consumed in India is in the form of cigarettes, whereas 40% of the tobacco used is in the form of bidis and the remaining 40% is consumed as chewing tobacco, pan masala, snuff, masheri ,gutkha and tobacco toothpaste. These products contain lime, catechu, putrefied tobacco, paraffin, areca nut and even many carcinogenic agents.

India is the second largest producer of tobacco in the world and further it ranks fourth in total tobacco consumption. The important reason implicated for the high economic burden in India is because of the availability of the various forms of tobacco.

The sex specific ratio of tobacco users in India

Type of tobacco users	Male (%)	Female (%)
Tobacco users	46.5	13.8
Smokers	29.3	2.4
Chewers	28.1	12.0

EPIDEMIOLOGY OF SMOKING IN PSYCHIATRIC PATIENTS

Comorbid Drug Abuse and Mental illness:

The lifetime prevalence of substance use disorder (abuse or dependence) including alcohol in patients with schizophrenia ranges from 10% to 60% [19].The Epidemiologic Catchment Area (ECA)study reported that 46% of patients with schizophrenia have some serious health problem with substance use during their lifetime compared with 16% of that in the general population . [20] The nicotine use rates in these patients range from 58% to 90% [21].

Of illicit substances, patients with schizophrenia preferentially use cannabis [22] , although cocaine abuse is also common, especially in the inner cities[23]. Similar to the general population, men are disproportionately represented among patients who use substances.

Smoking and Depression:

Much evidence supports an association between depressive symptomatology and smoking. It has been found in few studies that smokers exhibit higher rates of depression than the nonsmokers[24] and that the depressed persons experience greater difficulty quitting as compared to nondepressed, smokers[25]. Even subclinical levels of depression are associated with decreased latency to first cigarette following a quit attempt[26].

Smoking and Other Chemical Dependence

Rates of smoking among abusers of other drugs are higher than those in the general population, with estimates ranging from 75% to 90% [27]. Comorbidity is associated with increased health problems [28], as well as smoking and smoking cessation behaviors. Alcoholic smokers often tend to smoke more heavily and are found to experience lesser success in achieving abstinence than their nonalcoholic counterparts [29].

NICOTINE DEPENDANCE AND SCHIZOPHRENIA

Regarding the association between cigarette smoking and schizophrenia various facts have been proposed and the findings include the following:

1. The rate of smoking is at least 2 to 3 times higher in schizophrenia patients that in the general population

2. Schizophrenic patients who smoke, do so at heavier rates than that in the general population
3. Most of the smoking schizophrenic patients start smoking in their teens and many of them did so before the illness begins

Further few researchers have explained that nicotine dependance in schizophrenic patients is a method invented by patients themselves to "Self-medicate" their illness.The various neurocognitive dysfunctions of schizophrenia like attention ,cognition and information processing deficits are the prime symptoms that are being targeted by this nicotine dependance . The reasons offered include:

1. Disease aspects leading more patients to smoke
2. Smoking has been thought of to be an independent aetiological factor in schizophrenia rather than mere co-occurrence.
3. The possibility of genetic and environmental factors that predispose to both smoking and the disease.

Few authors have explained that the higher frequency of current smoking schizophrenic patients could be a summation of a higher initiation rate added on to a lower rate of quitting smoking. And further since most patients with schizophrenia begin to smoke before the onset of the schizophrenic illness, it has been postulated that persons prone to develop schizophrenia had a high vulnerability to starting smoking

.Other authors like Freedman et al. (1997) have described the presence of a neurophysiological abnormality that was genetically determined in patients with schizophrenia and their relatives, which was thought to be corrected atleast temporarily by a high peak of nicotine.

Based on exposure to tobacco, patients with schizophrenia are most vulnerable to adverse health consequences. Surprisingly, despite the high exposure to tobacco smoke, a number of reports suggest a lower rate of lung cancer and other malignancies in schizophrenic patients than in the population at large [30] . On the other hand, a study by Lichtermann[31] based on Finland's National Hospital Discharge and Disability Pension registers linked to the Finnish Cancer Registry, showed a higher rate of cancer (particularly of the lung) among schizophrenic individuals than in the population at large. The Finnish study also examined rates of illness among first-degree relatives of schizophrenic patients and found a lower-than-expected risk of cancer.

Lichtermann hypothesizes that access to cigarettes (eg,smoking policies on psychiatric units), rates of institutionalization, access to medication, and population genetic variations may all contribute to differences with other published studies. Apart from cancer risk, individuals with schizophrenia suffer higher death rates from cardiovascular and respiratory disease [32]. Therefore the weight of

evidence points toward increased health risks from smoking as a result of increased smoking rates in schizophrenia.

One Indian study that examined the non-biological factors influencing the prevalence of smoking in schizophrenia and stated that the rates of smoking in schizophrenic patients was higher than in patients diagnosed to have major affective disorders and other non-psychotic disorders and the reasons cited include family imposed restrictions on smoking and the lack of economic independence in these patients.They concluded with remarks of the need to consider the influence culture and social practices could have upon the behaviour.

ROLE OF SMOKING IN SCHIZOPHRENIA:SYMPTOM CORRELATES

Smoking has been suggested to be a marker of greater severity of schizophrenic illness .The correlations between fagerstorms nicotine dependance scores and the total of the negative symptom scores in schizophrenia has been found to be a significantly positive one, with no signficant associations with positive symptoms however [33]. Further, symptoms like impairement in attention, thinking, impulse control and orientation, and the scores on SANS- negative symptom subscales like blunted affect, social withdrawal ,stereotyped thinking and difficulty in abstract thinking , has been positively correlated with the severity of

nicotine dependence.Few contrary studies stated that smoking schizophrenia patients display less negative symptoms compared to non smoking schizophrenia patients [34].

Also, smokers may have higher scores on brief psychiatric rating scale due to more severe symptoms.It may also be that, patients with schizophrenia smoke with nicotine inorder to self medicate their disease ,where nicotine may help by regulating a dysfunctional mesolimbic dopamine pathway.

Positive and negative symptoms may be alleviated due to the supposedly nicotine caused increase of dopamine release in pre frontal cortex.There has been reports of psychotic symptoms worsening on nicotine withdrawal. There are reports of enhancement of cognitive performance on nicotine administration.

However, smoking schizophrenia patients, in general report the same reasons as other smokers, and offer reasons like the need to feel “addicted”, “relaxed” and “to calm down” with only a meager 17% of them reporting improvement of psychotic symptoms on smoking. This is a point against the self medication hypothesis put forward by few researchers.

In one of the most recent studies conducted in India ,association has been found between higher positive symptom scores and tobacco use, with however no significant differences in cognitive measure among nicotine non dependant and dependant patients. [35]

SENSORY GATING AND PREPULSE INHIBITION IN SCHIZOPHRENIA

Sensory Gating (P50) Deficit

Sensory gating refers to the centrally mediated inhibition of neuronal response to a redundant sensory input. There is reduced inhibition in schizophrenia of the neuronal responses to redundant sensory input as first noted by Lawrence E. Adler et al. in acutely psychotic, unmedicated schizophrenia patients. Sensory gating is studied in the laboratory using scalp EEG.

Robert Freedman, Adler, and Sherry Leonard provided evidence for linkage of the P50 sensory gating phenotype to chromosome 15q14 in schizophrenia pedigrees. Subsequently, an association of P50 deficit in schizophrenia with allelic variants in the promoter region of the α-7 nicotinic cholinergic receptor subunit gene on the 15q locus was described. .The drug probe studies also further support the role of low-affinity nicotinic receptors in the P50 gating abnormality in schizophrenia.

Prepulse Inhibition (PPI)

In the presence of a sudden, intense sensory input (e.g., loud sound), humans reflexively startle. The startle reflex consists of contractions of skeletal and facial muscles that is observed across species and meant to be a defensive response. The startle reflex is muted or inhibited in the presence of a preceding, weak sensory stimulus (prepulse). This muting of the startle response by prepulse is called prepulse inhibition and is observed when the prepulse occurs 30 to 500 milliseconds before the pulse (i.e., the intense stimulus eliciting the startle reflex). The maximum inhibition occurs between 60 and 120 milliseconds of interstimulus interval. Investigators have argued that PPI is a brain mechanism by which the nervous system screens or gates out the milieu noise in order to process salient aspects of the environment. In this context, the more salient the prepulse, the stronger it inhibits the startle response to pulse. Schizophrenia patients generally show normal startle response; however, this patient group shows reduced inhibition of the startle response by the prepulse compared to healthy control subjects.

A defect in the neuronal nicotinic acetylcholine receptor expression-genotypic or phenotypic has been implicated in the neuropathophysiology of schizophrenia. Smokers without schizophrenia have increased nicotinic receptor binding in postmortem brain hippocampus, caudate and cortex with increasing tobacco use.Whereas ,

schizophrenic smokers have reduced nicotinic receptor levels and this finding is indicative of an abnormally regulated high-affinity neuronal nicotinic receptors after the initiation of nicotine use.

One important theory that links schizophrenia and tendency for nicotine addiction is the presence of abnormalities in **auditory sensory gating** in patients with schizophrenia. Sensory gating is being mediated by functions of the α-7 nicotinic cholinergic receptor [36]. Nicotine in all its forms (smoking and smokeless) improves abnormal sensory gating in humans and animals.

The cognitive and neurophysiological deficits postulated to be improved with nicotine include : (1) abnormalities in smooth pursuit eye movements (2) sensory gating (3) transient normalization of the P50 inhibition abnormality(especially by high doses of nicotine) in both schizophrenic patients as well as their relatives (4) working memory and selective attention performance and (5) selective enhancement of visuospatial working memory in smoking schizophrenics. However, a study by Harris et al., stated that nicotine mainly affects attentional deficits without as much effects on other aspects of neurocognition like memory,learning , visuospatial or constructional abilities. [37]

SELF MEDICATION HYPOTHESIS IN SCHIZOPHRENIA

Smoking might be having a beneficial effect in schizophrenia by improving atleast to a certain extent its symptoms and also by decreasing the antipsychotics induced extrapyramidal side-effects and this is the core concept of 'the self-medication hypothesis' [38].

As discussed earlier the improved symptoms include cognitive functions like focused attention, sustained attention and aspects of memory like working memory, short-term memory and recognition memory. Studies using evoked potentials (P50 paradigm) and prepulse inhibition of the acoustic startle reflex suggest that deficient preattentive information processing, a core feature of schizophrenia illness, is improved following treatment with nicotine. Smoking can also improve extrapyramidal secondary effects of antipsychotic medication by virtue of its capacity to induce cytochrome P4501A2, an enzyme system involved in the metabolism of several antipsychotics and by causing few biological changes in the neurotransmitter systems of the brain.

ANTIPSYCHOTIC INDUCED MOVEMENT DISORDERS:

The incidence of antipsychotic induced parkinsonism is lesser in nicotine dependant schizophrenic patients who smoke cigarettes or use other forms of tobacco and the need for use of prophylactic anticholinergic medication is lower in neuroleptic - exposed patients with schizophrenia who smoke . The plausible explanation is thus that nicotine

enhances central dopaminergic activity and thus corrects the hypofunctioning of the central dopaminergic hypofunction in nigrostriatal dopamine systems produced by dopamine antagonists and hence decreases the incidence of antipsychotic induced parkinsonism.

Further a higher prevalence of Tardive Dyskinesia in smokers than non-smokers has been found [39]. The proposed mechanisms include 1)increased dopaminergic activity from nicotine[40] leading to nigrostriatal hypersensitivity to dopamine 2) neurotoxicity from the free radicals in cigarette smoke leading on to a damage to catecholaminergic neurons in the basal ganglia. 3) smoking induced increased risk of cerebrovascular pathology.[41]

SMOKING AND ANTIPSYCHOTICS

It has reported in studies that smoking is more frequent among young male patients with schizophrenia,in those who have an earlier onset of illness,and those who more often require inpatient management either by reason of the severity of symptoms or due to poor drug compliance and they often require higher doses of antipsychotic medication to achieve symptom remission.

Since cigarette smoke causes metabolic induction, they tend to consistently receive higher doses of antipsychotics[42]. By reason of its effects on antipsychotic medications , schizophrenic smokers display

lesser negative symptoms and also lesser parkinsonism than non-smokers with schizophrenia.

BLOOD LEVELS OF ANTIPSYCHOTIC MEDICATIONS

Clinical improvement in schizophrenia is affected by cigarette smoking, by its lowering of blood antipsychotic medication levels.The hydrocarbon agents in smoking and not nicotine per se are known liver enzyme inducers (effected through cytochrome P450 1A2 isoform induction) and hence increase drug metabolism – those of neuroleptics , anti anxiety and anti depressants. There has been documentations in studies that blood levels of neuroleptics like fluphenazine & haloperidol are lowered by upto 50% due to smoking. As per reports of some clinical epidemiological studies, smokers are prescribed higher neuroleptic doses than those who don't smoke.

The effect of schizophrenia treatment with haloperidol and clozapine on smoking behaviour , as studied by Mc Evoy et al[43], is that haloperidol treatment resulted in increased smoking and increase in blood levels of nicotine, when compared to the medication free baseline conditions. Further in a similar group of smokers with schizophrenia ,the smoked cigarette numbers and the expired air- carbon monoxide amount decreased following a clozapine treatment for 12 months , when compared to baseline measures during haloperidol treatment.

It is interesting to note that treatment with clozapine improves P 50 auditory evoked response gating. This fact suggests that , through this effect on sensory gating, clozapine treatment might be modulating the smoking behavior.Not only this, clozapine can also enhance the hippocampal acetyl choline levels.As a result of this acetylcholine-enhancing effect, patients on clozapine have near normal levels of P50 suppression.Acetyl choline levels are also increased by ondansetron, a 5HT3 antagonist.Similar to clozapine,P 50 sensory gating is enhanced in schizophrenic patients by ondansetron also. Donepezil, an Acetyl Choline esterase inhibitor, enhanced P 50 sensory gating in such patients[44]. .

MANAGEMENT OF SMOKING IN SCHIZOPHRENIA

Although smoking cessation may be more difficult for people with schizophrenia than for others [45], clinicians still should discuss the hazards of smoking and encourage patients to reduce their cigarette consumption. Some evidence suggests that group therapy combined with a nicotine patch may be effective in helping patients with schizophrenia reduce smoking[46].

Cigarette smoking among these patients may be more than just a ‘‘bad habit,’’ however[47]. One small study showed that haloperidol was associated with an increase in smoking and nicotine levels, whereas others suggest that switching treatment from typical antipsychotics to

clozapine may lead to a decrease in smoking . A controlled study suggested that atypical antipsychotic medications may facilitate smoking cessation more than typical agents.

Few studies have reported that outpatients with schizophrenia often reported retrospectively a decrease in smoking(ie. decreased daily cigarette consumption) after such patients are treated with the atypical antipsychotic clozapine compared to their smoking status when they were treated with typical antipsychotics like haloperidol ,chlorpromazine etc. [48]

Data also are emerging about the beneficial effects of bupropion combined with psychotherapy on nicotine addiction in this patient population . In the case of severely addicted patients, the advisable medications include: combined nicotine gum and patch therapy; bupropion combined with either nicotine patch , nicotine inhaler or nicotine nasal spray [49] .

A recent publication on the management of acutely disturbed and agitated patients with schizophrenia advises that smoking status should be included in the assessment of agitation and nicotine replacement should be included in the treatment of those who are smokers which helps in bringing down the agitation in such patients [50].

The Food and Drug Administration for tobacco-dependence treatment approved five different types of nicotine-replacement

therapies— viz . nicotine polacrilex (gum), the nicotine transdermal patch, nicotine inhaler, nicotine nasal spray, and the nicotine lozenge— all with nearly similar efficacies and with a very low overall risk for abuse liability [51]. Both the nicotine patch and bupropion have been found to be tolerated well and to improve outcomes in schizophrenia in small studies.

Pharmacologic and psychosocial interventions may be useful in assisting patients to reduce smoking and ultimately, it is hoped, smoking-related disease and mortality.

AIM OF THE STUDY

To study the prevalence and severity of Nicotine dependance in Schizophrenic patients and to study the clinical correlates in relation to the severity of dependence like Positive and Negative symptoms,antipsychotics induced abnormal involuntary movements and to compare it among nicotine dependant and non-dependant patients.

Objectives of the Study

1. To study the prevalence and severity of Nicotine dependance in Schizophrenic patients and its association with the duration of illness, Duration of Untreated Psychosis(DUP) and to compare it among the study(nicotine dependant) and control group(non – nicotine dependant patients)
2. To compare between the two groups ,the symptom correlation with the severity of nicotine dependance:
    a. Positive symptoms
    b. Negative symptoms
3. To compare the Chlorpromazine equivalents of various antipsychotics used to treat Schizophrenic patients with and without nicotine dependence .

4. To study about the incidence of antipsychotic induced abnormal involuntary movements –akathisia, drug induced parkinsonism and tardive dyskinesia among the two groups.

Study Design:

A cross-sectional case-control study of 30 cases and 30 control male outpatients with Schizophrenia.

Period of study:

March 2011 to June 2012

Subjects:

- **Cases:** Schizophrenic patients with history of smoking and /or using smokeless tobacco
- **Controls:** Schizophrenic patients without history of smoking

Inclusion Criteria:

1. Patients who fulfilled the ICD -10 Research Diagnostic Criteria for schizophrenia and with history of smoking or smokeless tobacco use.
2. Male patients in the age group 15-50 years.
3. Patients who consented for the study.

Exclusion Criteria:

1. Past and current H/O of another Axis I disorder.
2. Co-morbid substance use.
3. Mentally retarded patients
4. Demented patients.

HYPOTHESIS

1. In Patients with Schizophrenia with nicotine dependence the duration of illness is longer than the control group(non nicotine-dependant).
2. Patients with Schizophrenia with nicotine dependance have a longer duration of untreated psychosis(DUP) .
3. The severity of smoking is higher for smoking tobacco users than the users of smokeless tobacco.
4. Patients with Schizophrenia with nicotine dependance have significantly higher scores on the positive symptoms scale of Schizophrenia .
5. Patients with Schizophrenia with nicotine dependance have significantly lower scores on the negative symptoms scale of Schizophrenia.

6. Patients with Schizophrenia with nicotine dependance need higher doses of antipsychotics(Chlorpromazine equivalents) to treat their psychotic symptoms.
7. Patients with Schizophrenia with nicotine dependance more often develop symptoms of drug induced Tardive dyskinesia.
8. Patients with schizophrenia who smoke have lesser prevalence of drug induced extrapyramidal symptoms.
9. Patients with schizophrenia who smoke have lesser prevalence of drug induced akathisia as compared to those who do not smoke.

MATERIALS AND METHODS

Setting:

This study was carried out in the Out patient Section of the Department of Psychiatry, Tirunelveli Medical College Hospital.This hospital is the tertiary level referral centre for the urban and rural population of Tirunelveli.The study was approved by the Ethical Committee of Tirunelveli Medical college.A formal written consent in the mother tongue was obtained from all participants included in the study.All participating patients were given the information sheet pertaining to the nature of study.

Tools used:

1. Semi-Structured Proforma to collect Sociodemographic data,Family History, Disease type, age at onset of smoking,age at onset of illness,H/O recent treatment of medication induced movement disorders and its details,H/O abstinence,Reasons for smoking,duration of illness,age at start of treatment for the illness,treatment details including drug doses.
2. Nicotine dependence was measured by
    a. Fagerstorm's Test for Nicotine Dependence (FTND) for smoking tobacco-cigarettes and beedis.

b. The Fagerstörm's Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST)

3. The symptoms were measured by
    a. Scale for Assessment of Positive Symptoms(SAPS)
    b. Scale for Assessment of Negative Symptoms(SANS)

4. Abnormal Involuntary Movements were assessed using:
    a. Barney's Akathisia Scale(BAS)
    b. Modified Simpson Angus Scale(MSAS)
    c. Abnormal Involuntary Movement Scale(AIMS)

Statistical Analysis:

Central tendencies and the dispersion of the variables were studied using descriptive statistical methods such as mean, standard deviation.The study group (Nicotine dependent) and control group (Nicotine non users) were matched in respect of their demographic ,socio and economic status to identify the confounding of SED (Socio Economic and Demographic) variables. The matching was performed according to the type of variables by either Parametric or Non- parametric test such as Students 't' or χ^2 test. The prevalence of Nicotine dependence was identified by comparing the two groups in respect of their Schizophrenia characteristics by respective test of significance. The relationship

between the Nicotine dependence with smokers in respect SAPS and SANS was studied by Spearmans' rank correlation test among the Nicotine dependence subjects. The above statistical procedures were performed by the statistical package IBM SPSS statistics 20. The P - values less than 0.05 ($P<0.05$) were treated as significant in two tail condition.

Fagerstorms Test for Nicotine Dependance(FTND) [52]

The FTND is a short scale comprising of 6 items which quantify nicotine dependance. The smoking rate and the time lag between waking and the first cigarette is being scored 0 to 3.If the patient smokes fewer cigarette per day and if he takes a longer time for his first cigarette of the day he gets a lower score.The other 4 variables which are rated in a dichotomous manner include are smoking even while he is ill, having difficulty in refraining from smoking in places where it is forbidden , smoking cigarettes more heavily especially in the mornings and having difficulty in giving up the day's first cigarette.These variables are scored as yes (1) or no (0). The overall scores for severity of dependance : 0–2 :very low dependance , 3–4: low dependance , 5 :moderate dependance, 6–7 :high dependance, 8–10: very high dependance.

The Fagerstorm Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST)[53] is similar to the FTND scale and this scale measures the severity of using smokeless tobacco by estimating the number of

pouches/tins or cans used instead of the number of cigarettes smoked..It is scored in the same manner as FTND.

SAPS (Scale for the Assessment of positive Symptoms) and SANS (Scale for the Assessment of negative symptoms) These scales were sourced from the University of Iowa press, 1983.These scales were developed by Nancy Andreasen. These scales are used for the assessment of positive and negative symptoms, principally those occurring in schizophrenia. Both the instruments are used in a way complimentary to each other. They have been widely used in many studies and well tested for reliability and validity. The SAPS contains 35 items divided into 5 domains i.e. Hallucinations, Delusions, Bizarre behavior, Positive formal thought disorder and inappropriate affect. The SANS contains 24 items divided into 5 domains i.e. Affective flattening or blunting, Alogia, Avolition-apathy, Anhedonia-asociality and Attention. Items in both the scales are scored between 0 (none) and 5 (severe).

Barney's Akathisia Scale[54]

Using this scale patient is examined while they are sitting, standing, while talking about a neutral topic for a minimum of two minutes in each position. The subjective symptoms should also be elicited by direct interrogation.The scores are based on the Objective Akathisia, Subjective Awareness of Restlessness and Distress. The scores are given on a 4 point scale from 0 – 3 .Total score ranges from 0 to 9.

Modified Simpson Angus Scale[55]

It is a 10-item rating scale to assess for the presence of neuroleptic induced parkinsonism.One item measures gait hypokinesia, 6 items measure rigidity at the various body regions and 3 items measure glabella tap, tremor and salivation. Each item is rated on a 5-point scale of severity : 0 = normal to 4 = most severe. This scale has good internal consistency ,reliability . Inter-rater reliability was also good.

Abnormal Involuntary Movement Scale[56]

This scale has 12 items, each rated on a five-point severity scale ranging from 0 to 4. Ten items assess the abnormal movements in different body regions like orofacial area, extremities, and trunk, the global severity; two items rate the dental conditions which can make the diagnosis of dyskinesia difficult.It is a highly reliable and valid tool.

RESULTS & OBSERVATIONS

Table-1

Table showing the comparison of **Age distribution** and **Educational Status** of Study and Control groups .

S.No.	Variable	Cases(N=30)		Controls(N=30)		Statistics
		n	%	n	%	
1.	**Age group(years)**					t value= 0.289
	20-24	1	3.4	1	3.4	
	25-29	7	23.3	7	23.3	
	30-34	6	20.0	5	16.6	
	35-39	7	23.3	7	23.3	
	40-44	6	20.0	8	26.7	
	45-49	3	10.0	2	6.6	
	Mean ± S.D.	34.9±6.8		35.4±6.5years		
2.	**Education**					
	Uneducated	4		4		χ^2 =3.393 df=4
	Primary	9		7		
	High School	13		13		
	Hr. Sec	4		3		
	Graduate	0		3		

*p<0.05

The study and control groups were compared in the above table -1. The mean ages ±Standard Deviation of the study group and control group were 34.9±6.8 and 35.4±6.5years respectively. The t value was 0.289 and the difference was statistically not significant ($p>0.05$).

In the above table-1, the education was matched and there was no significant difference between the two groups ($p>0.05$).

Table -2

Table showing comparison of the **sociodemographic status** among the study and control group.

S.No	Variable	No of persons		Statistical Test	
		Cases (N=30)	Controls (N=30)		
		n	n	χ^2	Significance
1.	**Occupation**				
	Employed	7	9	0.341	p>0.05
	Unemployed	23	21	df=1	
2.	**Social class**				
	Low	28	28	0.0	p=1
	Middle	2	2	df=1	
3.	**Family history**				
	Yes	12	10	1.153	p>0.05
	No	18	20	df=1	
4.	**Type of Family**				
	Nuclear	15	15	0.0	p=1.00
	Joint	15	15	df=1	
5.	**Marital status**				
	Married	11	15	1.343	p>0.05
	Un married	13	9	df=3	
	Single	4	4		
	Divorced	2	2		

The two groups were matched in respect of their occupation ($p>0.05$), social class ($p=1.00$), family history ($p>0.05$), family type ($p=1.00$),the marital status($p>0.05$).

The study (Nicotine dependant) and control (non Nicotine dependant) groups were matched in respect of their age, education, occupation, social class, family history, type of family and marital status. The results revealed that they were not significantly different and hence they were comparable.

Table 3

Table showing the comparison of the **Duration of illness** between study and control groups:

S.No.	No. of years	Study Group (N=30)		Control Group (N=30)		t value
		n	%	n	%	
1.	0-10	6	20	10	33.3	0.671
2.	11-20	15	50	18	60	
3	21-30	9	30	2	7.3	
	Mean± S.D.	13.5±7.9		12.3±5.8		

*p<0.05

The duration of illness was compared between the study and control groups . Thus the mean duration of illness among nicotine dependant study group was 13.5±7.9 and the mean among the non nicotine dependant control group was 12.3±5.8. The difference between the duration of illness in the two groups was not significant.

Table 4

Table showing the comparison of **Duration of Untreated Psychosis(DUP)** between the study and control group:

Months	Study group(N=30)	Percentage	Control Group (N=30)	Percentage
	N	%	N	%
≤5	0	0	3	10
6-11	3	10	9	30
12-17	7	23.3	4	13.3
18-24	9	30	14	46.6
≥ 25	11	36.6	0	0

Among the nicotine dependant group, about 67% of the patients presented after 18 months of onset of their illness and none of them presented within 6 months of onset of illness.Whereas in the control group only 47% presented after 18 months of onset of illness.

Table 5

Table comparing the **Duration of Untreated Psychosis(DUP**) between the study and control group

No. of years	Study Group (N=30)		Control Group(N=30)		Statistical test
	n	%	n	%	
<1	3	10	12	40	χ^2 =
1-2	16	53	18	60	5.688
>2	11	37	0	0	df=2

$p<0.05$

The duration of untreated psychosis between the study and control group was compared in the above table 5 and the difference was found to be statistically significant.$p<0.05$.Thus the duration of untreated psychosis was significantly longer in the nicotine dependant group.

Table:6

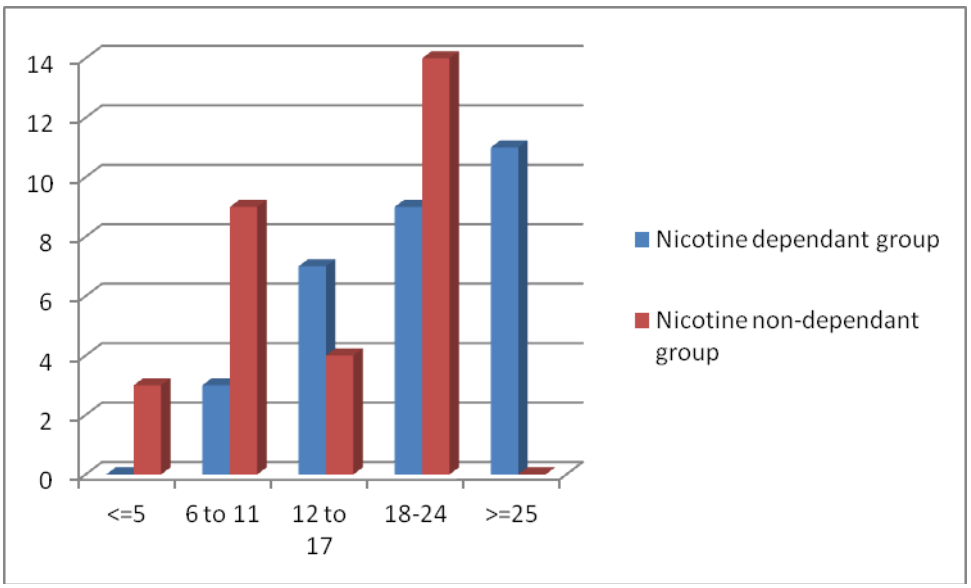
Table showing **Severity of nicotine dependance** among smoking and smokeless tobacco users

FTND& FTND-ST Score	Degree of dependance	Nicotine dependant (smoking) group(N=30)	Percentage %	Nicotine dependant (smokeless)group (N=30)	Percentage %
0-2	very low	5	16.6	19	63.3
3-4	Low	4	13.3	5	16.6
5	Medium	1	3.3	0	0
6-7	High	6	20	2	6.6
8-10	very high	14	46.6	4	13.3

It was found from the above table that about 66.6 % of the nicotine dependant group of the smoking type had high to very high dependence for nicotine.Whereas in the users of smokeless tobacco about 63.3% had very low dependence for nicotine.

Duration of untreated Psychosis

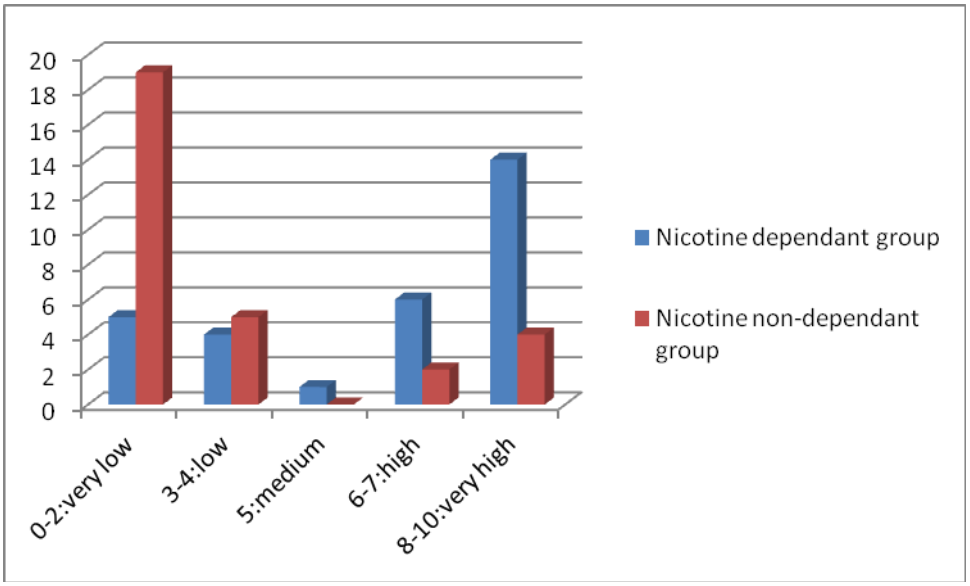
Frequency



Months

Severity of nicotine dependance

Frequency



Fagerstorm s scores

Table-7

Table showing the Prevalence of Nicotine dependence among users of smoking tobacco and smokeless tobacco.

Category	Number of persons(N=30)		χ^2
	Nicotine dependance	Non nicotine dependance	
	n	n	
Smoking tobacco	26	4	9.075^{**} df=1
Smokeless tobacco	14	16	

** $p<0.001$

The Prevalence of Nicotine dependence among users of smoking tobacco and smokeless tobacco is shown in the above table-7. The nicotine dependence among the two types of tobacco use was compared and the χ^2 was 9.075 with a significance of $p<0.001$.This showed that more patients using smoking tobacco were dependant on it as compared to the dependance in smokeless tobacco users.

Clinical Correlates of Nicotine dependence in Schizophrenia:

The two groups were compared in respect of their Duration of Untreated Psychosis(DUP), Positive symptoms (SAPS mean score), Negative symptoms (SANS mean score) and Chlorpromazine(CPZ) equivalents in table 8.

Table-8

Table showing the comparison of Clinical correlates between Study and Control groups.

S.NO	Clinical Correlates	Cases (N=30)		Control (N=30)		Difference b/w means	't'
		Mean	SD	Mean	SD		
1	Duration of untreated Psychosis (months)	20.9	8.5	15.1	8.3	5.8	2.684*
2	SAPS	11.3	4.6	5.5	2.7	5.8	6.004**
3	SANS	13.1	4.6	9.8	3.8	3.3	3.102*
4	CPZ equivalents	783.3	343.5	428.3	226.9	355.0	4.723**

df=58 $p<0.001$** $p<0.05$*

The above table 8 compares the clinical correlates between the groups. The mean durations of untreated Psychosis of study and control groups were 20.9±8.5 and 15.1±8.3 respectively and the difference between means was statistically significant ($p<0.05$).The mean SAPS score were 11.3±4.6 and 5.5± 2.7 respectively and difference between means was statistically highly significant ($p<0.001$). Similarly the means of SANS score between the two groups were 13.1± 4.6 and 9.8±3.8 respectively and the difference was also statistically significant ($p<0.05$). The means CPZ equivalents of study and control groups were 783.3±343.5 and 428.3±226.9 respectively and the difference between the two groups was statistically highly significant ($p<0.001$).

Relationship between Nicotine dependence with Positive (SAPS) and Negative (SANS) symptoms:

Table -9

Table showing the Correlation between Nicotine dependence with SAPS and SANS scores.

Variable	Rank Correlation "r"	r2	% of r^2
Positive symptoms	0.415	0.172	17.2*
Negative symptoms	0.013	0.000169	0.0169

*p<0.05

The above table -11 shows the correlation of positive and negative symptoms scores of study group with the severity of nicotine dependence. The results revealed that nicotine dependence was significantly and positively correlated with their positive symptoms.Hence 17.2% positive symptoms were depending upon the nicotine dependence. The Nicotine dependence was not significantly correlated with their negative symptoms (p>0.05)

Table -10

Table showing the comparison of abnormal involuntary movement-Tardive Dyskinesia between two groups.(AIMS scale scores)

AIMS scores	Number of persons			χ^2
	Study Group N=30	Control Group N=30	Total	
Positive	7	1	8	5.192*
Negative	23	29	52	df=1

*p<0.05

The study group and control group were compared in respect of their abnormal involuntary movement scales for Tardive dyskinesia in table-10. The Positive Score abnormal involuntary movement was significantly associated with Nicotine dependent group (p<0.05).

Table 11

Table comparing the scores of abnormal involuntary movement-drug induced extrapyramidal symptoms(Modified Simpson Angus Scale scores) of the two groups:

MSAS Score	Study Group N=30	Control Group N=30	Statistical test
<3	5	11	χ^2 =2.131
>3	25	19	df=1

*p<0.05

The two groups were compared in respect of their Modified Simpson Angus Scale scores for drug induced parkinsonism in table-11.A score <3was a normal score(absence of drug induced extrapyramidal symptoms) and a score of >3 was indicating the presence of drug induced extrapyramidal symptoms. The score was not significantly different among the study and control group (p>0.05)

Table -12

Table showing the comparison of Akathisia (Barne's Akathisia scale scores)between two groups.

BAS Scores	Number of persons			χ^2
	Study Group N=30	Control Group N=30	Total	
No akathia	23	19	42	1.758 df=2
Questionable	5	6	11	
Mild	2	5	7	

*$p<0.05$

The drug induced extrapyramidal symptoms-Akathisia between the study group and the control were compared and shown in the above table-12. The results revealed that there was no significant difference in the Barne's Akathisia scores between the two groups ($p>0.05$).

DISCUSSION

This study was conducted in the outpatient department of the Department of Psychiatry,Tirunelveli Medical College Hospital.Ethical committee approval for conducting the study was obtained from the Institutional Ethical committee in February 2011(annexure).The study was carried out in the period between March 2011 and September 2012.

The cases and controls were selected based on the selection criteria and the sample was selected by stratified random sampling.An information sheet(annexure) regarding the illness, the smoking patterns and the purpose of the study was provided to the patient.Informed consent was obtained in the mother tongue. For illiterate patients the contents were read out and then written consent was obtained(annexure).Only those patients who consented to participate in the study and were co-operative for interview were recruited.

The study and control subjects were matched in respect of their age, education, occupation, social status, family history, type of family and marital status and found that they were not significantly different ($p>0.05$). And hence the two groups were not confounded with the above attributes. They were comparable study subjects.

Prevalence of smoking and duration of illness:

The duration of illness was compared between the study and control groups .The mean duration of illness among nicotine dependant study group was 13.5±7.9 and the mean among the non nicotine dependant control group was 12.3±5.8. The mean of the duration of illness among smokers was higher than the control group. The difference between the two means was not significant. Among the study group 30%(n=9) had the longest duration of illness(21-30)years as against 13%(n=2) in the control group.Thus patients with very long duration of illness tend to be nicotine dependant.This implies that all patients with a longer duration of illness should be screened for nicotine dependence and suitable deaddiction choices be offered.

Prevalence of nicotine dependence among different types of tobacco users:

The dependence rates for the various types of tobacco used by our study group for cigarettes and beedis was 54%, for chewing /smokeless tobacco in the form of ganesh tobacco,shanthi tobacco ,paan masala it was13%.Patients with very low to low dependence usually chewed tobacco and spit it out after about an hour or so while the highly dependant group both chewed and swallowed it.Patients who used both accounted for 33% of the dependant group.This is closer to the values quoted in a study among psychiatric population by Praba Chandra et

al(2005) ,NIMHANS which stated that smoking Beedis - 56% was more than the use of cigarettes -30%.According to their study the commonest type of tobacco used was Chewing tobacco -67% and Cigarettes or beedis (with chewing) -45% while in our study population it was 13%(pure chewing tobacco) and both smoking and chewing type 33%.Hence we infer that the prevalence of chewing tobacco as a substance of dependence is much lower when compared to that reported by other Indian studies done on a heterogenous population including both north and south Indian patients.In a study by Srinivasan and Thara in 2002,the prevalence of smoking among male schizophrenic patients using both Cigarettes or beedis (with chewing) was 31.6% which is much closer to our results of 33%.

In the study group patients ,among the smokers,13%(n=4) were non-dependant on cigarette or beedis and among the smokeless tobacco users 52%(n=16)were non dependant on chewing type of tobacco.The difference of nicotine dependance among the two groups(smoking and smokeless tobacco users) was statistically significant ($p<0.001$) .The prevalence of nicotine dependance among both smoking and smokeless forms of tobacco is 66%.This is twice that of the prevalence of the general population as quoted in a study by Subramanian et al in (2004). Rates of nicotine use in schizophrenic patients have been reported to range from 58% to 90% according to Hughes et al(1986).

Smoking prior to onset of Schizophrenia:

Further 83% of the patients started smoking prior to the onset of schizophrenia.This is slightly lesser than the value noted in a study by Ciara Kelly & Robin McCreadie(2000) which stated that almost 90% of patients had begun to smoke before schizophrenic illness onset . Further it is more than that noted by Zhang XY et al(2012) in their study among Chinese population which showed that 73% smoked prior to their illness onset.

Number of years smoked prior to onset of schizophrenia:

Regarding the average number of years smoked prior to the onset of schizophrenia,among nicotine dependant patients in our study population it was found to be 7.5 years with a standard deviation of 5.86.This appears to be very close to that noted by Zhang XY et al(2012) in their study among Chinese population which showed that the majority of patients in their study smoked 7.6 years prior to the onset of their illness .

Age at onset of Illness:

In the nicotine dependant group, the average age at which schizophrenic illness had started was 22.1±4.9 years while it was 20.4±2.7 years in the non nicotine dependant group.This difference might be accounted for as an indirect evidence of the self medication hypothesis which states that schizophrenics may smoke to alleviate

atleast partially some of their troubling psychotic symptoms. Since many of the smoking patients begin their habit before the onset of the illness, a common vulnerability to both the disease and the dependance has been proposed. The reduction of positive symptoms by long term nicotine use is probably by a potential correction of the dissociated cortical–subcortical dopamine activity that occurs in schizophrenia . However in the severe cases of schizophrenia ,'self-medication', even with greater amounts of nicotine has not been found to be effective.

Duration of Untreated Psychosis(DUP)

Among the nicotine dependant group,about 67% of the patients presented to treatment after 18 months of onset of their illness.Whereas in the control group only 47% presented after 18 months of onset of illness.

The duration of untreated psychosis in the study group was >2 years in 37% among the nicotine dependant patients while none of the patients in the control group had DUP of >2years.The difference of DUP between the two groups was statistically significant.($p<0.05$)

Although there are numerous confounding factors having a role to play in influencing DUP other than smoking viz

- *Gender*:: males have a long duration of untreated psychosis than females

- *age at onset of illness:* longer DUP was significantly related to younger age at onset of illness[57]
- *baseline symptoms*: longer DUP to be associated with higher levels of at least some aspects of negative or deficit symptoms at presentation
- *premorbid adjustment:*lower premorbid adjustment to be significantly associated with longer duration of untreated psychosis .
- *treatment response* :Shorter duration of untreated psychosis generally predicts a better response to antipsychotic treatment.

Since our study group and control group were matched based on socio-demographic variables and it was a homogenous group of male schizophrenics,the difference in DUP between the two groups may be linked to nicotine dependence.

Reasons attributed:

The most common reasons attributed by smokers for smoking included the need to reduce the hearing of voices and to reduce suspiciousness :37%, to decrease confusion &distress :17%, to feel energetic &to reduce dullness : 13%, to reduce irritability :10%, habit, to relax :7%

Thus there is some data to support the self medication hypothesis that smoking improves positive and negative symtoms of schizophrenia from the reasons given by the smokers.

SEVERITY OF NICOTINE DEPENDANCE

- **The severity of dependence:**
- **to smoked tobacco**:47% -severe
- **to smokeless tobacco:13%**-severe

We find that about 66.6 % of the nicotine dependant group of the smoking type had high to very high dependence for nicotine.Whereas in the users of smokeless tobacco about 63.3% had very low dependence for nicotine.Past studies indicated that 68% of schizophrenic smokers were found to be heavy smokers who smoked in an average more than 25 cigarettes daily compared with only 11% of the general population who smoke.Thus we see that the severity of nicotine dependence though being twice of that in the general population,is still lower than the rates of severity which is quoted in the western population studies. In one of the Indian studies on tobacco use in male schizophrenic patients, the prevalence of smoking was about 38% .In the study by Praba et al at NIMHANS(2005) it was found that 63% of the entire study population which included smokers with different psychiatric diagnosis had moderate to severe nicotine dependence.

From our study we see that the rate of tobacco use among Indian psychiatric patients is lesser than that reported in the western population . While in the west almost one-half to two-thirds of all psychiatric patients smoke it is not so in our population.It is actually difficult to interpret these cross-cultural variations, because they probably reflect the numerous confounding variables such as culture, income , population distribution and availability and cost of tobacco products. For instance, , in India unlike that in the west there is a strong family system, even for the psychiatrically ill individuals. Family members who take care of the patients impose genuine restriction on smoking which results in lower rates of using tobacco in its various forms among the Indian schizophrenia patients. The meagre income for patients in our population if at all they are employed may also limit their affordability to buy commercially-prepared tobacco products.

However there have also been few studies that show that the rates of smoking appear to be high in affective disorders(Praba Chandra et al). Another study states that rates of smoking were higher in subjects with schizophrenia as with other psychotic disorders. Further the severity of smoking covaried with depression over time [58].

Clinical Correlates:

SAPS and SANS scores:

The duration of Psychosis among the Nicotine dependence Schizophrenia was significantly greater than (20.9±8.5 >15.1±8.3 months) non Nicotine dependence Schizophrenia. The SAPS of the Nicotine dependence Schizophrenia was significantly greater than (11.3±4.6 > 5.5± 2.7) non Nicotine dependence Schizophrenia. The SANS of the Nicotine dependence Schizophrenia was significantly greater than (13.1±4.6 > 9.8±3.8) non Nicotine dependence Schizophrenia.These findings are closely similar to the earlier studies which stated that smokers have more severe symptoms with higher scores on the Brief Psychiatric Rating Scale.

Chlorpromazine Equivalents:

The Chlorpromazine Equivalents of the antipsychotics used in Nicotine dependence Schizophrenia was significantly greater than (783.3±343.5 > 428.3±226.9) non Nicotine dependence Schizophrenia. Individuals with schizophrenia who smoke are found to receive higher doses of antipsychotics than non-smokers . Thus the cytochrome p450 inducing effect of nicotine upon antipsychotic metabolism is inadvertently corrected by psychiatrists. Longitudinal studies comparing atypical antipsychotics with typical antipsychotics showed that the latter

are associated with increased smoking in some individuals , with a greater difficulty for quitting smoking too.George et al.(2000) reported that many schizophrenic patients reported a decrease in daily cigarette consumption after treatment having been treated with clozapine compared to their use when they were treated earlier with typical antipsychotics. Meszaros ZS et al (2011) [59] in their study findings have stated that in patients with schizophrenia both conventional antipsychotic drugs and severe, treatment resistant schizophrenia is associated with heavy smoking .

Symptom correlation with Nicotine dependence:

The symptoms of Positive (r=0.415) and Negative (r=0.456) were significantly ($p<0.01$) positively correlated with Nicotine dependence of Smokers. The Nicotine dependence of smokers determined the positive symptoms 17.2% (% r^2) and negative symptoms were neither lower nor higher. Hence although the SANS mean score in the two groups differed in a statistically significant manner, there was no correlation with the severity of nicotine dependence.

Our study does not support the findings by Patkar et al(2002) which showed that there was significant positive correlations found between Fagerstrom scores and the total negative symptom scores.They further observed that smoking was not significantly associated with

positive symptoms.[60]The study by Zhang XY et al (2012)showed that smokers with schizophrenia tend to display lesser negative symptoms scores than non-smokers with schizophrenia [61] . Thus the possible beneficial effect of nicotine on the schizophrenic symptoms and on the antipsychotic induced movement disorders gets obscured by the higher incidence of severe nicotine dependance in the more severe forms of schizophrenia.

Drug induced Abnormal Involuntary movements:

Tardive dyskinesia:The Positive score of Abnormal involuntary movement scale was significantly different between the study and control group.($p<0.05$).Our results are similar to that by Yassa et al. who reported that the prevalence of tardive dyskinesia was higher among smokers than that among nonsmokers with schizophrenia who are under treatment with neuroleptic medication. There has also been a study contradictory to this by Goff et al. which reported that the propensity to develop tardive dyskinesia was lower as measured by the lower Abnormal Involuntary Movement Scale score among smokers in comparison with non smokers.

Drug Induced Parkinsonism: The two groups were compared in respect of their Modified Simpson Angus Scale scores for drug induced parkinsonism in table-11. The score was not significantly different

among those with Nicotine dependence or the nicotine non-dependant group ($p>0.05$). This result refutes the earlier studies which states that parkinsonism caused by prolonged antipsychotic use is lesser in patients who smoke cigarettes, and that the use of prophylactic anti cholinergic medicines to prevent such drug induced parkinsonism is significantly lower in neuroleptic- exposed schizophrenia patients who smoke .However comparison of the dose and duration of anticholinergic use was not an objective in our study.

Akathisia:The results revealed that there was no significant difference between two groups in terms of the Barne's akathisia scores ($p>0.05$).There was a speculation by Wirshing et al who states that not only does long-term smoking exposure cause dyskinesia, but even acute exposure to nicotine may actually increase dyskinetic movements in prone individuals .However our study have no evidence to support this.This could be probably because most of our patient were chronic patients who might have been earlier been treated for akathisia and their symptoms might have abated.

Thus from the detailed analysis of our findings we come to understand that nicotine dependant schizophrenics had a longer duration of illness and a longer duration of untreated psychosis.A huge majority of the nicotine dependant patients had started smoking before the onset of

illness and the age of onset of schizophrenia was later than the non dependant patients.We found that most of the nicotine dependent patients used smoking forms of tobacco and the severity of dependance was also higher among them when compared to smokeless tobacco users. Both the positive and negative symptoms were higher in the nicotine dependant schizophrenics ,the positive symptoms correlated positively with the severity of smoking while the negative symptoms did not correlate with the severity of nicotine dependance.The nicotine dependant schizophrenics further needed higher chlorpromazine equivalent doses and also had higher prevalence of tardive dyskinesia.However the nicotine dependant schizophrenics had extrapyramidal symptoms as equally as the non dependant patients.

LIMITATIONS OF OUR STUDY

There are few limitations in our study

1. One limitation which though ethically appropriate was the exclusion of patients who had severe psychiatric instability in the form of severe symptomatology, violent or assaultive behaviour, uncooperativeness due to suspiciousness or gross disorganization etc . Such patients would have been even more vulnerable to tobacco use in its many froms, and having omitted such patients from our study population may mean that the prevalence rates reported herein actually underestimates the prevalence and severity of tobacco use and dependence.
2. The absence of another control group from the general population in our study which if we had included would have helped us analyse the difference in prevalence in the psychiatrically ill patients and the normal population at large.
3. Exclusion of other substance abuse grossly limited the number of patients who would have been severely dependant on nicotine.
4. This being a cross sectional missed out the effects of the substance use on various stages of illness and with varying types of drugs prescribed in different periods.

5. Since females were not included in the study we are unable to generalize our findings to the whole psychiatric population. Exploring substance use among the female population would have given the gender comparisons and also helped understand the trend of substance use among female patients.

6. Since we could not determine drug levels by laboratory methods the actual drug level measured as chlorpromazine equivalents could not be confirmed objectively.This is especially important because most of the psychiatric patients do not strictly adhere to the dosing regimens and have poor drug compliance.

CONCLUSION

The oft quoted assertion that smoking is the most commonly encountered preventable cause of premature morbidity and mortality in the world raises important questions for the psychiatrist who is the most sought physician for the treatment of substance dependant patients.Apart from the physical risks associated with smoking,it has been implicated in the increased mortality in schizophrenia.The association between smoking and schizophrenia is a long drawn debate whether one leads to another or if both have common neurobiological underpinnings.

In the recent years the need to increase the attention focused on improving the care of patients with co-occurring mental illness and cigarette smoking or other substance use disorders has been thoroughly felt even in the developing country like India. This physically underserved population require the use of evidence-based approaches to improve both the symptoms due to mental illness as well as to enable a smooth abstinence from drugs of abuse . This type of dual diagnosis is important because, smoking modifies psychiatric symptoms, alters the blood level of prescribed drugs and further serves as a clue for the presence of dependance for other substance of abuse.

The findings from our study include:

1. In Patients with Schizophrenia with nicotine dependence the duration of illness is longer than the control group but the difference was not statistically significant .
2. Patients with Schizophrenia with nicotine dependance have a significantly longer duration of untreated psychosis(DUP) .
3. The severity of smoking is significantly higher for smoking tobacco users than the users of smokeless tobacco.
4. Patients with Schizophrenia with nicotine dependance have significantly higher scores on the positive symptoms scale of Schizophrenia .
5. Patients with Schizophrenia with nicotine dependance have significantly **higher scores** on the negative symptoms scale of Schizophrenia.
6. Patients with Schizophrenia with nicotine dependance need higher doses of antipsychotics(Chlorpromazine equivalents) to treat their psychotic symptoms.
7. The prevalence of drug induced Tardive dyskinesia in patients with Schizophrenia with nicotine dependance is significantly higher as compared to the control group.
8. The prevalence of drug induced extrapyramidal symptoms **did not differ** significantly between the two groups.

9. The prevalence of drug induced akathisia **did not differ** significantly between the two groups.

Our study demonstrates that there is a definite association with the severity of nicotine dependence and the disease state.Also it shows that most of the smokers needed higher doses of antipsychotic medication to ameliorate their symptoms. A few of them are more prone to develop abnormal involuntary movements due to their smoking.This study demonstrates that smoking be accorded a top priority in the treatment of people with schizophrenia since the lives of these patients are considerably deranged with tobacco use by increase of both morbidity and mortality .However, our study having been done on stable out-patients with schizophrenia ,may in future help the treating psychiatrist to select which individuals are more likely to improve their schizophrenic symptoms and their extrapyramidal side effects using the upcoming nicotine patches or other nicotine agonists which are under clinical trials for treatment of cognitive dysfunctions in schizophrenia.

- A significant proportion of the schizophrenic smoker's meagre income is spent on cigarettes especially in rehabilitation setups. It has been estimated that most schizophrenics who smoke afford to spend more than a third of their monthly disability income on cigarettes .It is a common sight in most residential institutions for

mentally ill patients that patients do work inorder to earn for their cigarettes.Hence other ways of contingencies may be entertained.

- The huge problem after treatment of schizophrenic patients is reintegration into the community. Smoking will definitely have an influence on the community integration because they will have lesser income to spend on their everyday needs like clothing ,housing etc.
- Stigma for both smoking and schizophrenia can reduce chances for success in obtaining a new employment ,in housing and may limit the scopes for renewed peaceful interpersonal relationships which have been put to strain due to the burden of illness and institutionalisation.

Patients with schizophrenia have the real need to be offered treatment for one of the most common substance of dependence namely nicotine and it is our duty to protect their physical health.This study under scores the need to **plan smoking cessation regimens for patients with Schizophrenia which might offer better control of clinical symptoms** at the same time **prevent the morbidity** associated with heavy smoking among the recovering patients and aid a **better psychosocial rehabilitation.**

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Appendix II – Semi Structured proforma

Prevalence and Clinical correlates of Nicotine Dependence in Schizophrenia

Investigation Questionnaire

Principal Investigator: Dr. M. Amali Victoria, PG-MD Psychiatry, Tirunelveli Medical College.

1.Name		2. Sex & Age	☐Male ☐ Female ☐ Transgender Age : _____
3. Education	☐Uneducated ☐ Primary ☐ High school ☐Secondary ☐ Graduate	4. Occupation	☐Employed ☐ Unemployed ☐
5. Socio-economic status	☐Low ☐ Middle ☐ High	6. Family history	☐Yes ☐ No 7. Age at onset
8. Marital status	☐Married ☐ Separated ☐ Divorced ☐ Widow ☐ Unmarried	9. Type of family	☐Nuclear ☐ Joint
10.Diagnosis	☐Paranoid ☐ Hebephrenic ☐ Catatonic ☐ Undifferentiated ☐ Simple	11. Duration of Untreated Psychosis	☐1-6mon ☐ 7-12mon ☐ 13-18mon ☐ 19-24mon ☐ >24months
12. Mode of Treatment	☐Typical antipsychotics ☐ Atypical ☐ ECT	13. Treatment Name of the drugs : Dose:	
14. Medication Side Effects		☐Yes ☐No If Yes quote:	
15.Number of admission/OP visits for abnormal involuntary movements since the start of treatment		☐Admission : ____ ☐OP : _____	
16. Number of years you smoked		i.Prior to the onset of illness	ii.Since the onset of illness
17.Reason for smoking			
18. Any periods of abstinence		☐Yes ☐ No If Yes quote:	
19. Whether treated for nicotine dependence		☐Yes ☐ No If Yes quote:	

Appendix III SAPS

Scale for Assessment of Positive Symptoms (SAPS)

0 = None; 1 = Questionable; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe

Hallucinations	**0**	**1**	**2**	**3**	**4**	**5**
1. Auditory Hallucinations	☐	☐	☐	☐	☐	☐
2. Voices Commenting	☐	☐	☐	☐	☐	☐
3. Voices Conversing	☐	☐	☐	☐	☐	☐
4. Somatic or Tactile Hallucinations	☐	☐	☐	☐	☐	☐
5. Olfactory Hallucinations	☐	☐	☐	☐	☐	☐
6. Visual Hallucinations	☐	☐	☐	☐	☐	☐
7. Global Rating of Hallucinations	☐	☐	☐	☐	☐	☐
Positive Formal Thought Disorder	**0**	**1**	**2**	**3**	**4**	**5**
8. Derailment	☐	☐	☐	☐	☐	☐
9. Tangentiality	☐	☐	☐	☐	☐	☐
10. Incoherence	☐	☐	☐	☐	☐	☐
11. Illogicality	☐	☐	☐	☐	☐	☐
12. Circumstantiality	☐	☐	☐	☐	☐	☐
13. Pressure of Speech	☐	☐	☐	☐	☐	☐
14. Distractible Speech	☐	☐	☐	☐	☐	☐
15. Clanging	☐	☐	☐	☐	☐	☐
16.Global Rating of Formal Thought Disorder	☐	☐	☐	☐	☐	☐
Inappropriate Affect	**0**	**1**	**2**	**3**	**4**	**5**
17. Inappropriate Affect	☐	☐	☐	☐	☐	☐

Bizarre Behavior	**0**	**1**	**2**	**3**	**4**	**5**
18.Clothing and Appearance	☐	☐	☐	☐	☐	☐
19.Social and Sexual Behavior	☐	☐	☐	☐	☐	☐
20.Aggressive &Agitated Behavior	☐	☐	☐	☐	☐	☐
21.Repetitive or Stereotyped Behavior	☐	☐	☐	☐	☐	☐
22.Global Rating of Bizarre Behavior	☐	☐	☐	☐	☐	☐
Delusions	**0**	**1**	**2**	**3**	**4**	**5**
23.Persecutory Delusions	☐	☐	☐	☐	☐	☐
24.Delusions of jealousy	☐	☐	☐	☐	☐	☐
25.Delusions of Guilt or Sin	☐	☐	☐	☐	☐	☐
26.Grandiose Delusions	☐	☐	☐	☐	☐	☐
27.Religious Delusions	☐	☐	☐	☐	☐	☐
28.Somatic Delusions	☐	☐	☐	☐	☐	☐
29.Delusions of Reference	☐	☐	☐	☐	☐	☐
30.Delusions of Being Controlled	☐	☐	☐	☐	☐	☐
31.Delusions of Mind Reading	☐	☐	☐	☐	☐	☐
32.Thought Broadcast	☐	☐	☐	☐	☐	☐
33.Thought Insertion	☐	☐	☐	☐	☐	☐
34.Thought Withdrawal	☐	☐	☐	☐	☐	☐
35.Global Rating of Delusions	☐	☐	☐	☐	☐	☐

Total Psychoticism Score : _____

Total Disorganization Score: _____

Appendix IV SANS

Scale for Assessment of Negative Symptoms (SANS) **0 = None; 1 = Questionable; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe**													
Affective Flattening or Blunting	**0**	**1**	**2**	**3**	**4**	**5**	**Avolition – Apathy**						
1) Unchanging Facial Expression	☐	☐	☐	☐	☐	☐	13) Grooming and Hygiene	☐	☐	☐	☐	☐	☐
2) Decreased Spontaneous Movements:	☐	☐	☐	☐	☐	☐	14) Impersistence at Work or School	☐	☐	☐	☐	☐	☐
3) Paucity of Expressive Gestures	☐	☐	☐	☐	☐	☐	15) Physical Anergia	☐	☐	☐	☐	☐	☐
4) Poor Eye Contact:	☐	☐	☐	☐	☐	☐	16) Global Rating of Avolition – Apathy	☐	☐	☐	☐	☐	☐
5) Affective Non-responsivity:	☐	☐	☐	☐	☐	☐	**Anhedonia – Asociality**	☐	☐	☐	☐	☐	☐
6) Lack of Vocal Inflections	☐	☐	☐	☐	☐	☐	17) Recreational Interests and Activities	**0**	**1**	**2**	**3**	**4**	**5**
7) Global Rating of Affective Flattening	☐	☐	☐	☐	☐	☐	18) Sexual Activity	☐	☐	☐	☐	☐	☐
Alogia	**0**	**1**	**2**	**3**	**4**	**5**	19) Ability to Feel Intimacy and Closeness	☐	☐	☐	☐	☐	☐
8) Poverty of Speech:	☐	☐	☐	☐	☐	☐	20) Relationships with Friends and Peers	☐	☐	☐	☐	☐	☐
9) Poverty of Content of Thought	☐	☐	☐	☐	☐	☐	21) Global rating of Anhedonia – Asociality	☐	☐	☐	☐	☐	☐
10) Blocking	☐	☐	☐	☐	☐	☐	**Attention**	☐	☐	☐	☐	☐	☐
11) Increased Latency of Response	☐	☐	☐	☐	☐	☐	22) Social Inattentiveness	☐	☐	☐	☐	☐	☐
12) Global Rating of Alogia	☐	☐	☐	☐	☐	☐	23) Inattentiveness during Mental Testing	☐	☐	☐	☐	☐	☐
TOTAL NEGATIVE SYMPTOM SCORE: _____							24) Global Rating of Attention	☐	☐	☐	☐	☐	☐

Appendix V Fagerstorm's Test for Nicotine Dependence (FTND) for smoking tobacco-cigarettes and beedis.

Fagerstrom's Test for Nicotine Dependence

1. How soon after you wake up do you smoke your first cigarette?		☐ After 60 minutes[0] ☐ 31-60 minutes [1] ☐ 6-30 minutes [2] ☐ Within 5 minutes [3]
2. Do you find it difficult to refrain from smoking in places where it is forbidden?		☐Yes [1] ☐ No[0]
3. Which cigarette would you hate most to give up?		☐The first in the morning[1] ☐ Any other [0]
4. How many cigarettes per day do you smoke?		☐10 or less[0] ☐11-20[1] ☐21-30[2] ☐31 or more[3]
5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?		☐Yes [1] ☐ No[0]
6. Do you smoke even if you are so ill that you are in bed most of the day?		☐Yes [1] ☐ No[0]
Your score		Interpretation of score-
0-2 Very low dependence		
3-4 Low dependence		
5 Medium dependence		
8-10 Very high dependence		

Appendix VI Fagerstörm's Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST)

Fagerström's Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST)

1. How soon after you wake up to do you place your first dip?		☐ Within 5 min [3] ☐ 6–30 min [2] ☐ 31–60 min [1] ☐ After 60 min [0]
2. How often do you intentionally swallow tobacco juice?		☐ Always [2] ☐ Sometimes [1] ☐ Never [0]
3. Which chew would you hate to give up most?		☐ The first in the morning[1] ☐ Any other [0]
4. How many cans/pouches per week do you use?		☐ More than 3 [2] ☐ 2 to 3 [1] ☐ 1 [0]
5. Do you chew more frequently during the first hours after awakening than during the rest of the day?		☐ Yes [1] ☐ No[0]
6. Do you chew if you are so ill that you are in bed most of the day?		☐ Yes [1] ☐ No[0]
Your score		Interpretation of score-
0-2 Very low dependence		
3-4 Low dependence		
5 Medium dependence		
8-10 Very high dependence		

Appendix VII Barneys Akathisia Scale

Name:_____ **Date:**_____

Barnes Akathisia Rating Scale (BARS)

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

Global Clinical Assessment of Akathisia

0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1 *Questionable.* Non-specific inner tension and fidgety movements
2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Scoring the Barnes Akathisia Rating Scale (BARS)

The Barnes Akathisia Rating Scale is scored as follows:

Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9.

The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.

(BAS)

Appendix VIII Modified Simpson Angus Scale(MSAS)

Patient Name:_____ Rater Name and Date: _____

MODIFIED SIMPSON-ANGUS SCALE (MSAS)

Extrapyramidal Side Effects Scale

Each item is rated on a 5-point scale of severity (0 = normal; 4 = most severe; NR = not rated). Circle the rating that best describes the subject's present condition (3 is upper limit for patients without EPS).

1. Gait: The patient is examined as he walks into the examining room: his gait, the swing of his arms, his general posture all form the basis for an overall score for this item. This is rated as follows:

0 = Normal
1 = Diminution in swing while the subject is walking
2 = Marked diminution in swing with obvious rigidity in the arm
3 = Stiff gait with arms held rigidly before the abdomen
4 = Stooped, shuffling gait with propulsion and retropulsion
NR = Not ratable

2. Arm Dropping: The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's Syndrome, the arms fall very slowly.

0 = Normal, free fall with loud slap and rebound
1 = Fall slowed slightly with less audible contact and little rebound
2 = Fall slowed, no rebound
3 = Marked slowing, no slap at all
4 = Arms fall as though against resistance, as though through glue
NR = Not ratable

3. Shoulder Shaking: The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner, who also grasps one hand and also clasps the other around the subject's elbow. The subject's upper arm is pushed to and fro, and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:

0 = Normal
1 = Slight stiffness and resistance
2 = Moderate stiffness and resistance
3 = Marked rigidity with difficulty in passive movement
4 = Extreme stiffness and rigidity with almost a frozen joint
NR = Not ratable

4. Elbow Rigidity: The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted overall but not rated as a separate item.)

0 = Normal
1 = Slight stiffness and resistance
2 = Moderate stiffness and resistance
3 = Marked rigidity with difficulty in passive movement
4 = Extreme stiffness and rigidity with almost a frozen joint
NR= Not ratable

5. Wrist Rigidity or Fixation of Position: The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion, and ulnar and radial deviation, or the extended wrist is allowed to fall under its own weight, or the arm can be grasped above the wrist and shaken to and fro. A "1" score would be a hand that extends easily, falls loosely, or flaps easily upwards and downwards.

0 = Normal
1 = Slight stiffness and resistance
2 = Moderate stiffness and resistance
3 = Marked rigidity with difficulty in passive movement
4 = Extreme stiffness and rigidity with almost a frozen joint
NR = Not ratable

6. Head Rotation: The subject sits or stands and is told that the examiner will move his head from side to side, that it will not hurt, and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain.) Clasp the subject's head between the two hands with the fingers on the back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to this movement.

0 = Loose, no resistance
1 = Slight resistance to movement
2 = Resistance is apparent and the time of rotation is shortened
3 = Resistance is obvious and rotation is slowed
4 = Head appears stiff and rotation is difficult to carry out
NR = Not ratable

Patient Name:_____ Rater Name and Date: _____

7. Glabella Tap: The subject is told to open his eyes and not to blink. The glabella region is tapped at a steady, rapid speed. Note the number of times that the subject blinks in succession. Take care to stand behind the subject so that he does not observe the movement of the tapping finger. A full blink need not be observed; there may be a contraction of the infraorbital muscle producing a twitch each time a stimulus is delivered. Vary the speed of tapping to assure that the muscle contraction is related to the tap.

0 = 0 to 5 blinks
1 = 6 to 10 blinks
2 = 11 to 15 blinks
3 = 16 to 20 blinks
4 = 21 or more blinks
NR = Not ratable

8. Tremor: The subject is observed walking into the examining room and then is re-examined for this item with his arms extended at right angles to the body and the fingers spread out as far as possible.

0 = Normal
1 = Mild finger tremor, obvious to sight and touch
2 = Tremor of hand or arm occurring spasmodically
3 = Persistent tremor of one or more limbs
4 = Whole body tremor
NR = Not ratable

9. Salivation: The subject is observed while talking and then asked to open his mouth to elevate his tongue.

0 = Normal
1 = Excess salivation so that drooling takes place if mouth is opened and tongue is raised
2 = Excess salivation is present and might occasionally result in difficulty in speaking
3 = Speaking with difficulty because of excess drooling
4 = Frank drooling
NR = Not ratable

10. Akathisia: The subject is observed for restlessness. If restlessness is noted, ask, "Do you feel restless or jittery inside; is it difficult to sit still?" Subjective response is not necessary for scoring, but subject report can help make the assessment.

0 = No restlessness reported or observed
1 = Mild restlessness observed, e.g., occasional jiggling of the foot occurs when the subject is seated
2 = Moderate restlessness observed, e.g., on several occasions, the subject jiggles his foot, crosses and uncrosses his legs, or twists a part of the body
3 = Restlessness is frequently observed, e.g., the subject's foot or legs are moving most of the time
4 = Restlessness persistently observed, e.g., the subject cannot sit still, might get up and walk
NR = Not ratable

TOTAL SCORE:_____

Total Score Severity:
Less than 3 = normal
3 to 5 = minimal degree of movement disorder
6 to 11= clinically significant degree of movement disorder
12 to 17 = severe degree of movement disorder is present

References:
Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 1970;212(Suppl 44): 11-19.

Hawley CJ, Finneberg N, Roberts AG, Baldwin D, Sahadevan A, Sharman V. The use of the Simpson Angus Scale for the assessment of movement disorder: A training guide. Int J Psych Clin Pract 2003; 7: 249-257.

Rush J (2000) Handbook of Psychiatric Measures. Washington: American Psychiatric Publishing.

Appendix XI Abnormal Involuntary movement Scale(AIMS)

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS) **0 = None 1 = Minimal, may be extreme normal 2 = Mild 3 = Moderate 4 – Severe**							
		0	**1**	**2**	**3**	**4**	
Facial and Oral Movements	1. Muscles of facial Expression e.g., movement of forehead, eyebrows,periorbital area, cheeks; include frowning, blinking, smiling, grimacing)	☐	☐	☐	☐	☐	
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	☐	☐	☐	☐	☐	
	3. Jaw e.g. biting, clenching, chewing, mouth opening, lateral movement	☐	☐	☐	☐	☐	
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	☐	☐	☐	☐	☐	
Extremity Movements	5.Upper (arms, wrists, hands, fingers). Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic).	☐	☐	☐	☐	☐	
	6. Lower (legs, knees, ankles, toes). (E.g., lateral knee movement, foot taping, heel dropping, foot squirming, inversion and eversion of foot.)	☐	☐	☐	☐	☐	
Trunk Movements	7. Neck, shoulders, hips (e.g., rocking, twisting, squirming, pelvic gyrations)	☐	☐	☐	☐	☐	
Overall Severity	8. Severity of abnormal movements:	☐	☐	☐	☐	☐	
	9. Incapacitation due to abnormal movements	☐	☐	☐	☐	☐	
	10. Patients awareness of abnormal movements (Rate only patients report No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	☐	☐	☐	☐	☐	
Dental Status	11. Current problems with teeth and/or dentures	☐Yes ☐ No					
	12. Does patient usually wear dentures?	☐Yes ☐ No					
	13. Edentia?	☐Yes ☐ No					
	14.Do movements disappear in sleep?	☐Yes ☐ No					

Instructions: Complete the examination procedure before entering these ratings

Scoring:

- Score the highest amplitude or frequency in a movement on the 0-4 scale, not the average;
- Score Activated Movements the same way; do not lower those numbers as was proposed at one time;
- A POSITIVE AIMS EXAMINATION IS A SCORE OF 2 IN TWO OR MORE MOVEMENTS OR a SCORE OF 3 OR 4 IN A SINGLE MOVEMENT
- Do not sum the scores:e.g. a patient who has scores 1 in four movements DOES NOT have a positive AIMS score of 4.

Appendix X Disease information form

ஆராய்ச்சித் தகவல் தாள்

திருநெல்வேலி அரசுப் பொது மருத்துவமனைக்கு வரும் மனச்சிதைவு நோயாளிகளிடம் நிலவும் புகைப் பழக்கத்தைப் (Nicotine dependence) **பற்றிய ஆராய்ச்சி இங்கு நடைபெற்று வருகிறது.**

மனச்சிதைவு நோயாளிகளிடம் நிலவும் புகைப் பழக்கத்தைப் பற்றி ஆய்வதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம்.இந்த ஆராய்ச்சியில் பங்கேற்பதால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு உள்ளாகாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களின் விருப்பத்தின் பேரில் தான் இருக்கிறது.மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்தச் சிறப்புப் பரிசோதனையின் முடிவுகள் ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பவர் கையொப்பம்**

தேதி

Appendix XI - Copy of Informed Consent

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சித் தலைப்பு : மனச் சிதைவு(schizophrenia) **நோயாளிகளிடம் நிலவும் புகைப் பழக்கத்தைப்** (nicotine dependence)**பற்றிய ஆய்வு**

பெயர் : **தேதி :**

வயது : **உள்நோயாளி எண் :**

பால் : **ஆராய்ச்சிச் சேர்க்கை எண் :**

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் எனக்கு முழுமையாகவும் தெளிவாகவும் விளக்கப் பட்டன.

எனக்கு விளக்கப் பட்ட விஷயங்களைப் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தருகிறேன்.

மனச் சிதைவு நோயாளிகளிட்ம் நிலவும் புகைப் பழக்கத்தைப் பற்றிய ஆய்வு என்னும் ஆராய்ச்சியில் பங்கேற்க நான் சம்மதம் தெரிவிக்கின்றேன்.

இந்த ஆராய்ச்சியில் பிறர் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் விலகலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னைச் சேர்த்துக் கொள்ளச் சம்மதிக்கிறேன்

கையொப்பம்

Appendix XII - Master Chart

Group	S.No.	Age	Education	occupation	Socio-economic status	Family history	Age of onset	Marital status	Type of family	Diagnosis	Duration of Untreated Psychosis	Duration group	Mode of treatment	Chlorpromazine equivalents	Medication Side Effects	Admission	OP	Hallucination	Positive	Bizarre Behaviour	Delusion	Total-SAPS	Blunted Affect	Alogia	Avolition	Anhedonia	Attention	Total-SANS	Fagestorm	Smoke Group	Fagestorm	Smokeless Group	AIMS Score	BARS score	MSAS Score	Smoking - prior	Smoking – post	Abstinence	Treatment for nicotine dependance	Reasons
1	1	30	S	U	L	Y	26	U	J	P	14	2	T	400	Y	0	3	4	2	1	4	11	3	2	5	3	1	14	5	3	6	1	N	0	2	9	4	N	N	to reduce dullness ,suspicio
1	2	30	P	U	L	N	25	S	N	P	24	3	T	800	N	0	0	5	4	3	5	17	3	2	4	3	3	15	9	4	8	1	N	0	3	0	2	N	N	AH reduction
1	3	25	H	U	L	Y	18	U	N	P	28	3	T	1000	Y	0	4	1	1	5	5	12	4	4	4	5	4	21	3	2	0	2	N	1	11	4	7	Y	N	to feel active
1	4	27	P	U	L	Y	22	U	N	P	28	3	T	900	y	0	4	4	4	5	5	18	2	1	5	4	1	13	6	3	10	1	N	0	5	14	7	N	N	Delusions dec
1	5	43	S	E	M	N	29	M	N	P	14	2	T	800	y	0	3	3	4	2	5	14	3	0	0	2	0	5	10	4	0	2	P	1	4	0	1	N	N	AH ,Delusions dec
1	6	29	H	U	L	Y	26	M	J	P	18	2	A	400	Y	0	0	5	2	4	5	16	4	3	4	3	1	15	10	4	2	1	N	0	2	1	2	Y	N	AH
1	7	31	H	U	L	N	26	M	J	C	20	2	A	400	N	0	0	1	4	5	5	15	1	4	4	4	3	16	6	3	0	2	N	0	5	5	5	N	N	to reduce tension&relax
1	8	34	H	E	L	Y	30	U	J	P	18	2	B	750	N	0	0	1	1	1	1	4	3	3	2	2	1	11	8	4	0	2	N	0	4	15	5	Y	N	to feel energetic
1	9	45	P	E	L	N	30	M	N	P	30	3	T	1100	N	0	0	5	1	4	5	15	3	4	4	4	3	18	6	3	0	2	N	0	1	13	12	N	N	Habit
1	10	41	U	U	L	N	17	U	J	P	6	1	B	700	Y	0	3	1	2	3	4	10	4	4	4	3	3	18	6	3	0	2	N	0	7	0	10	N	N	Delusions,confusions fear
1	11	40	U	U	L	N	34	M	N	P	24	2	B	1250	Y	0	2	4	3	3	0	10	1	1	2	1	1	6	9	4	0	2	P	0	2	14	2	N	N	AH
1	12	35	P	E	L	N	20	M	N	C	34	3	T,E	500	N	0	0	1	1	1	1	4	2	2	1	2	1	8	0	1	3	1	N	0	4	2	15	N	N	na
1	13	48	H	U	L	Y	38	S	N	P	32	3	B	1000	Y	0	1	5	5	2	5	17	3	2	3	1	1	10	10	4	0	2	P	0	3	16	10	N	N	avoids distraction
1	14	37	H	U	L	Y	35	D	N	P	10	1	B	500	N	0	0	4	0	0	4	8	3	3	3	2	1	12	0	1	4	1	N	0	2	10	2	y	N	confusion red
1	15	37	H	U	L	N	30	U	J	P	28	3	B	300	N	0	0	2	2	2	2	8	3	3	3	2	2	13	0	1	4	1	N	0	2	5	7	Y	N	na
1	16	37	U	U	L	N	30	U	J	C	26	3	B	300	Y	1	0	2	0	3	1	6	4	4	4	4	4	20	10	4	0	2	P	0	1	15	7	N	N	disterss red.

1	17	44	P	E	M	N	26	M	N	P	20	2	B	1100	N	0	0	0	0	0	1	1	1	1	2	1	2	7	9	4	0	2	N	0	2	6	18	N	N	na
1	18	43	H	U	L	Y	33	M	N	P	24	2	T	300	N	0	0	1	1	1	1	4	1	1	0	1	1	4	2	1	4	1	N	0	5	20	10	N	N	irritability red.
1	19	30	H	U	L	N	18	M	J	P	18	2	T	900	Y	0	2	1	1	1	5	8	2	1	4	2	1	10	7	3	0	2	N	2	3	4	10	N	N	Delusions red.
1	20	37	P	U	L	N	16	U	J	P	36	3	T	1250	N	0	0	4	3	2	1	10	3	3	2	1	2	11	0	1	9	1	N	0	5	0	3	N	N	na
1	21	32	P	U	L	N	17	U	J	P	12	1	T	1300	N	0	1	3	4	3	5	15	4	4	3	3	2	16	10	4	0	2	N	0	3	8	14	N	N	irritability red.
1	22	25	H	U	L	Y	18	U	N	P	6	1	T	600	Y	2	1	4	2	4	5	15	2	1	3	3	2	11	10	4	2	1	P	1	2	10	7	N	N	irritability red.
1	23	29	H	U	L	N	22	U	J	P	12	1	B	600	N	0	0	4	3	2	4	13	1	1	2	1	2	7	7	3	0	2	N	0	7	19	1	Y	N	fear,suspicion red.
1	24	23	S	U	L	N	18	U	J	P	18	1	T	800	N	0	0	5	3	4	5	17	3	2	3	3	3	15	10	4	10	1	P	1	3	0	1	N	N	na
1	25	28	H	U	L	Y	21	S	J	C	34	3	T	1200	Y	2	1	4	3	4	4	15	3	3	3	2	3	14	9	4	6	1	P	1	4	4	7	N	N	Ahred.
1	26	29	U	E	L	Y	24	M	N	P	14	2	A	300	N	0	0	3	4	3	4	14	3	3	4	4	3	17	4	2	4	1	N	0	2	6	5	N	N	to feel energetic
1	27	40	P	E	L	N	23	M	N	P	28	3	T	1250	Y	2	1	2	2	2	2	8	4	4	5	3	4	20	4	2	0	2	N	0	5	4	17	N	N	confusion red
1	28	36	P	U	L	N	30	S	N	C	26	3	B	700	N	0	0	3	3	3	3	12	3	3	2	2	3	13	8	4	0	2	N	0	1	3	6	N	N	AH reduction
1	29	45	S	U	L	N	25	U	J	P	12	1	T	700	Y	3	4	3	2	2	2	9	4	4	3	3	4	18	4	2	2	1	N	2	5	7	20	N	N	disterss red.
1	30	38	H	U	L	Y	28	D	J	P	14	2	T	1400	Y	2	1	3	3	3	1	13	3	3	3	4	3	16	8	4	0	2	N	0	4	10	10	N	N	AH reduction
2	1	48	G	E	M	Y	21	M	N	P	24	3	T	200	N	0	0	3	0	0	3	6	1	1	1	0	0	3	0	2	0	2	N	0	3					
2	2	29	H	U	L	N	25	S	N	P	5	1	B	500	Y	0	2	4	3	1	4	12	3	1	2	1	1	8	0	2	0	2	N	0	6					
2	3	43	G	U	L	N	42	M	N	P	6	1	A	200	N	0	0	4	2	1	4	11	3	3	4	2	1	13	0	2	0	2	N	0	3					
2	4	40	U	U	L	N	32	M	J	P	24	3	A	200	N	0	0	1	2	1	0	4	1	1	3	2	1	8	0	2	0	2	N	0	5					
2	5	33	H	E	L	N	23	M	N	P	6	1	T	700	y	0	1	1	4	4	3	12	1	1	1	1	1	5	0	2	0	2	N	2	8					
2	6	32	H	U	L	N	15	U	J	P	18	2	B	500	N	0	0	0	1	1	2	4	2	2	3	1	0	8	0	2	0	2	N	1	9					
2	7	29	H	U	L	N	19	U	J	P	6	1	T	1100	Y	1	2	1	1	1	1	4	1	1	1	1	0	4	0	2	0	2	N	2	10					
2	8	42	G	E	L	N	19	U	J	P	24	3	T	700	Y	0	3	0	2	2	2	6	0	0	1	0	1	2	0	2	0	2	P	2	9					
2	9	42	H	E	L	Y	30	M	N	P	13	2	T	400	N	0	0	0	0	0	2	2	1	1	0	0	0	2	0	2	0	2	N	0	1					
2	10	34	P	E	L	N	19	M	N	P	24	3	B	600	Y	0	0	3	2	1	3	9	4	3	4	3	1	15	0	2	0	2	N	0	5					
2	11	40	U	U	L	N	34	M	N	P	16	2	A	350	Y	0	2	2	1	1	0	4	4	2	2	3	1	12	0	2	0	2	N	0	6					
2	12	25	P	E	L	Y	20	M	N	C	6	1	A	200	N	0	0	1	1	1	1	4	2	3	1	2	1	9	0	2	0	2	N	0	4					
2	13	38	H	U	L	Y	28	S	N	P	24	3	T	700	Y	0	2	2	1	1	3	7	3	2	2	1	1	9	0	2	0	2	N	2	7					
2	14	42	H	U	L	Y	35	D	N	P	6	1	B	850	Y	0	1	2	0	0	3	5	3	3	2	2	1	11	0	2	0	2	N	1	6					
2	15	33	H	U	L	N	25	U	J	P	24	3	B	400	Y	1	2	2	0	1	2	5	2	1	3	2	2	10	0	2	0	2	N	2	8					
2	16	37	U	U	L	N	30	U	J	C	24	3	A	200	N	0	0	2	0	3	1	6	4	3	3	2	2	14	0	2	0	2	N	0	1					
2	17	45	P	E	M	N	26	M	N	P	20	2	B	400	N	0	0	1	0	0	1	2	1	1	2	1	2	7	0	2	0	2	N	0	2					
2	18	43	H	U	L	Y	33	M	N	P	4	1	T	300	Y	0	1	1	1	1	1	4	1	3	1	2	2	9	0	2	0	2	N	0	5					

2	19	30	H	U	L	N	19	U	J	P	12	2	T	350	Y	0	2	2	1	1	2	6	2	1	4	2	2	11	0	2	0	2	N	1	6
2	20	37	P	U	L	N	17	M	J	P	24	3	T	700	Y	0	1	2	1	2	1	6	3	3	2	1	2	11	0	2	0	2	N	0	6
2	21	28	P	U	L	N	22	M	J	P	6	1	T	400	N	0	0	3	0	1	2	6	4	2	3	2	2	13	0	2	0	2	N	0	5
2	22	25	H	U	L	Y	20	U	N	P	5	1	B	300	Y	0	1	2	1	2	1	6	3	2	3	2	2	12	0	2	0	2	N	0	3
2	23	39	S	U	L	N	22	U	J	P	24	3	T	500	Y	1	1	2	1	2	3	8	3	1	2	3	2	11	0	2	0	2	N	0	8
2	24	23	S	U	L	N	20	U	J	P	6	1	A	200	N	0	0	1	0	0	1	2	2	2	3	3	2	12	0	2	0	2	N	0	3
2	25	28	H	U	L	Y	21	S	J	C	24	3	B	400	Y	1	1	1	1	0	3	5	3	3	2	2	3	13	0	2	0	2	N	1	6
2	26	29	U	E	L	Y	24	M	J	P	12	2	A	200	N	0	0	0	0	0	2	2	2	1	2	2	1	8	0	2	0	2	N	0	2
2	27	40	P	E	L	N	23	M	N	U	24	3	T	200	Y	1	1	2	1	0	0	3	4	1	3	3	3	14	0	2	0	2	N	1	8
2	28	36	P	U	L	N	30	S	N	C	10	2	A	200	N	0	0	1	0	2	2	5	3	2	1	4	0	10	0	2	0	2	N	0	2
2	29	35	S	U	L	N	25	M	J	P	9	1	T	400	Y	0	1	2	0	0	2	4	3	4	3	2	4	16	0	2	0	2	N	0	6
2	30	38	H	U	L	Y	25	D	J	P	24	3	T	500	Y	0	1	1	0	1	3	5	2	2	1	5	3	13	0	2	0	2	N	1	6